American Journal of Obstetrics and Gynecology

VOL. 50 SEPTEMBER, 1945 No. 3

Original Communications

THE EFFECT ON INFANT MORTALITY OF VITAMIN K ADMINISTERED DURING LABOR*

EDITH L. POTTER, M.D., PH.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, the University of Chicago and the Chicago Lying-in Hospital)

WITH the discovery of vitamin K and the realization that in experimental animals spontaneous bleeding often occurred when the vitamin was absent from the diet, an interest in the possible relationship of vitamin K to bleeding in the newborn infant was immediately stimulated.

For many years hemorrhagic disease has been a subject of discussion. It was defined by Townsend in 1894 as spontaneous external or internal bleeding occurring in newborn infants, unrelated to trauma, accident, or definite disease, and this is the definition still widely used. The differences of opinion which exist concerning the incidence and mortality rates have arisen largely because of the difficulty in determining which hemorrhages are spontaneous and which are the result of some form of injury. There are no specific pathologic changes in hemorrhagic disease and the decision as to whether or not trauma is contributory to a hemorrhage seems often to be largely a matter of personal opinion.

Clifford, in a detailed discussion of hemorrhagic disease in 1939, stated that he believed the original definition should be followed, and excluded from this category "bleeding of traumatic origin in the central nervous system, liver, adrenals, etc.," but, "if the infant develops spontaneous external or internal hemorrhages in areas not directly related to the injury, the diagnosis of hemorrhagic disease is made." Likewise microscopical intracranial hemorrhage occurring in the absence of a history of trauma and associated with multiple hemorrhages in other areas was included in the classification. Using these criteria as a basis for diagnosis he concluded from the available literature that the disease occurred in from 1:118 to 1:333 births with a mortality of from 30 to 38 per cent. He found that the incidence and mortality rates both varied when the criteria demanded for the diagnosis were changed. If all types of intracranial hemorrhage were included, the mortality rose to approximately 70 per cent. If all infants with internal hemorrhage—brain, pulmonary, abdominal—were eliminated, the mortality was practically zero. Clifford in his own group of 69 cases had an incidence of 1:333 births with a 30 per cent mortality, or one death from hemorrhagic disease in every 1,000 deliveries.

*Presented before a regular meeting of the Chicago Gynecological Society, Nov. 17, 1944.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

Capon, who was among those that felt there was strong evidence that all internal hemorrhage was traumatic, stated: "In my experience gross bleeding into the suprarenal glands, the peritoneal cavity or under the capsule of the liver and spleen are generally of traumatic origin. I have not included any of these in my series although it must be admitted that any baby which has a greatly increased bleeding tendency may suffer internal hemorrhage from some slight trauma which would not affect a normal infant." He included as having hemorrhagic disease only those infants showing external hemorrhage from the gastrointestinal or urinary tracts, umbilicus, mucous membranes, or vagina, and was careful to exclude any with a history of trauma, asphyxia, sepsis, or syphilis. The incidence of hemorrhagic disease according to his conception was 1:520 with a mortality of 10.8 per cent, or one death from hemorrhagic disease in every 5,000 deliveries.

Rodda, on the other hand, was particularly impressed by cerebral hemorrhage as a manifestation of hemorrhagic disease and believed that it was frequently due to mild trauma accompanied by delayed coagulation and prolonged bleeding time. He gave figures from various small series of autopsies in which the incidence of intracranial hemorrhage as a cause of death ranged as high as 76 per cent, and stated that he himself believed these figures did not exaggerate the importance of intracranial hemorrhage as a cause of death, and that the majority of such hemorrhages could be prevented if the coagulation time of all newborn infants was determined and whole blood was given intramuscularly as a prophylactic procedure when the coagulation time was prolonged.

Following the publication of Rodda's paper in 1920, the question as to whether a prolongation of coagulation time is an essential feature of hemorrhagic disease has been repeatedly raised. Clifford, in 1939, stated that if only those cases where a prolongation could be demonstrated were included, hemorrhagic disease would be a rare condition of little importance. Sanford and Leslie, on the other hand, demanded a prolongation before making such a diagnosis, and in 1938 reported finding only two cases of true hemorrhagic disease among 5,500 newborn infants, an incidence of 1:2,750.

The discovery of vitamin K, the establishment of adequate methods of determining prothrombin levels, and the recognition that the vitamin is related to the amount of prothrombin in the blood gave a new impetus to the study of hemorrhagic disease.

Numerous investigators have shown that the prothrombin time is prolonged beyond the normal adult average in practically all infants from the second to the fifth day of life. Some, Javert and Moore, Snelling and Nelson, Hellman and Shettles, Brinkhous, Smith, and Warner have reported a prolonged prothrombin time in cord blood; but others, Webster and Fitzgerald, Richdorf and Kearney, Russell and Page, Valentine et al., Waddell and Guerry, Quick and Grossman, Nygaard, Owen et al. have found prothrombin time within the normal adult range at birth, with the prolongation starting toward the end of the first day and returning to relatively normal limits by the end of the first week. Fitzgerald and Webster stated that, although the prothrombin in cord blood may be low, other unknown substances cause cord blood to coagulate more rapidly than normal adult blood. Infants vary in the degree of prolongation, and there is no unanimity of opinion concerning the limit of physiologic prolongation and the beginning of a pathologic state. Although 30 per cent of normal is accepted by most investigators as definitely pathologic, many babies with levels considerably lower show no evidence of hemorrhage. The evidence (Hellman and Shettles, Kato and Poncher) suggests that premature infants are more subject to abnormalities of prothrombin time than are infants at term, but this has not been definitely proved. According to Webster and Fitzgerald the administration of barbiturates to the mother during labor causes an excessive prolongation of prothrombin time, but Hardwicke was unable to confirm this.

It has been shown that vitamin K has a definite effect in reducing the coagulation time when the prolongation is due to prothrombin deficiency. By giving vitamin K to infants immediately after birth, or by administering it to the mother within the twenty-four-hour period prior to delivery, this drop in prothrombin can be prevented.

Investigators have varied greatly in their recommendations concerning the dosage and preferable time of administration of vitamin K. Lawson recommended giving vitamin K daily to all pregnant women for one month prior to the expected date of delivery, and Valentine et al. attempted this form of administration although many of their mothers actually received the drug for much shorter periods. Mathews stated that it should be given all women for two weeks prior to delivery, that it should be continued for the first six days after delivery if the infant is breast fed, and that, in addition, the babies themselves should receive vitamin K in one large dose intramuscularly at birth or in small doses orally for six days. According to Hellman and Shettles it should be given daily for at least two weeks before delivery. Dam agreed on a two-week period of administration but thought it essential to give the last dose within two to twenty-four hours of delivery. Fiechter believed five to ten days of administration prior to labor was necessary to give normal levels. Snelling and Nelson at one time thought it advantageous to give vitamin K daily one or two days prior to delivery but subsequently concluded that one dose given after the onset of labor and two or more hours prior to delivery was sufficient. Poncher stated that since there is no evidence of a cumulative effect, giving it for more than one week prior to delivery was useless, and that adequate results could be obtained by giving a single dose at the onset of labor.

Many other investigators have concluded that one dose given to the mother during labor was sufficient to prevent a prolongation of the infant's prothrombin time. One of the largest series to show the effectiveness of a single dose was that of Webster and Fitzgerald. In agreement are Huber and Shrader, Mull et al., Beck et al., Bohlender et al., McReady et al., and Parks and Sweet. Fitzgerald and Webster found it effective when administered orally from forty-five minutes to twenty-six hours prior to delivery, or parenterally as late as fifteen minutes before delivery. McReady et al. believed the interval between administration and delivery should not exceed fifteen hours, Mull et al. tried to give it four to ten hours before delivery, Clifford thought there should be an interval of at least three hours, Huber and Shrader of at least two hours, while Bohlender et al. could find no difference in the effect when the interval range was from five minutes to twenty-four hours.

Although Shettles, Delfs, and Hellman thought they obtained a more uniform shortening in the prothrombin time of cord blood by maternal administration, and the comment has been made that intracranial and other forms of hemorrhage could more probably be prevented by giving the drug to the mother than to the infant, many investigators believe equal protection can be afforded by giving the vitamin to the mother or to the infant itself (Bruchsaler, Toohey, Fitzgerald and Webster), that if the mother had not received the vitamin it could be given the infant after birth (Huber and Shrader), while only a few have felt that administration to the infant itself was preferable (Richdorf and Kearney, Sanford et al.). Warner has reported that the amount of vitamin K required is so small as to be easily satisfied by prelacteal feedings of cow's milk, and Salomonsen and Nygaard, and Gellis and Lyon have been of much the same opinion. Russell and Page thought a 1 per cent vitamin K ointment rubbed into the skin gave adequate protection. Vollmer et al., on the other hand, stated that every infant should receive vitamin K (preferably through the skin) regardless of whether it had been given to the mother, and Waddell and Lawson reported that on their service the antenatal administration of the vitamin to the mother before labor was supplemented by giving it to the infant during the first few days of life. Clifford, too, stated: "To provide every possible protection in the light of our present knowledge and experience, every newborn baby could well be given vitamin K at birth whether or not there has been previous maternal administration."

After studying the work of many investigators it seems reasonable to conclude that the usual prolongation of prothrombin time in the blood of the newborn can ordinarily be prevented by giving a single dose of vitamin K to the mother during labor or to the infant after birth.

Although Fitzgerald and Webster, and Sanford et al. have shown a slight elevation of prothrombin in the blood of the mothers who received vitamin K, no appreciable maternal effect is to be expected from such medication. Portes and Varangot reported finding the longest prothrombin times in the mothers of the infants who showed the greatest prolongation, but most investigators have failed to find any correlation, and regardless of the degree of prolongation of the infant's prothrombin time, that of the mother has never been shown to be outside of the normal range.

The demonstration that prothrombin time is prolonged in many infants gave rise to the particular investigation of prothrombin time in hemorrhagic disease of the newborn infant. Although previous investigators had not been of the uniform opinion that the coagulation time was necessarily prolonged in hemorrhagic disease, new reports seemed to indicate that all infants on whom such a diagnosis was made had a prolonged prothrombin time, that this was shortened by the administration of vitamin K, and that the disease was cured. Since vitamin K given to the mother or infant would prevent prolongation of prothrombin time, and since the prevention of prolongation of prothrombin time was believed to mean prevention of hemorrhagic disease, a great many investigators (Ballon, Beck et al., Bohlender et al., Bruchsaler, Clifford, Dam, Fiechter, Hellman and Shettles, Huber and Shrader, McReady et al., Valentine et al., Webster and Fitzgerald) have recommended the routine prophylactic administration of vitamin K to all women during labor, and many have made amazing statements concerning the decrease in infant mortality which could thus be brought about.

Waddell and Lawson stated: "Every infant born at the University of Virginia Hospital is treated with vitamin K through the mother and this treatment is supplemented by oral administration of vitamin K in the first few days of life. Our experience convinces us that hypoprothrombinemia and associated neonatal hemorrhage will not occur in infants so treated and that so-called traumatic birth injury has been and will continue to be materially lessened." Mull et al. reported that "administration of the synthetic vitamin K to women in labor has been adopted as a routine procedure at the Maternity Hospital and the Cleveland City Hospital." Mathews believed that "routine use . . . will turn hemorrhagic disease into a thing of the past and will drop to nil this occurrence of babies normal at birth becoming idiots due to hemorrhagic disease in the first week." Kato and Poncher said: "While in some cases of intracranial hemorrhage birth trauma was the precipitating factor, the severity of the bleeding was apparently induced by a lowering of prothrombin level of the infant's blood. Since it is not possible by antepartum examination of the maternal blood to detect which infants will have a prothrombin deficiency the administration of vitamin K to the mother shortly before delivery is suggested." Javert was a little more conservative and suggested that "the prophylactic use of vitamin K therapy in mothers and their infants with prolonged labors, short severe labors, toxemia of pregnancy, and treated syphilis may lower the incidence of hemorrhagic disease and (non-traumatic) intracranial hemorrhage."

Sage startled his readers by the statement: "Vitamin K may well prove to be a life saver for 30,000 to 80,000 American babies annually." This seems a little optimistic in view of the fact that in the United States in 1940 only 67,866 babies died under one month of age. Lehmann, using the decrease in incidence of fatal intracranial hemorrhage in a group of infants receiving vitamin K after birth as compared to a similar group receiving none, concluded that the routine use of vitamin K should cause a decrease in mortality of 1.6 per 1,000 births, making a saving of 160 babies in the 100,000 born annually in Sweden.

Writing for a nonmedical audience Richardson stated: "It is fair to believe that the general use of this latest of the vitamins will be the cause of great reduction in our infant mortality. . . . The life-saving function of the newly discovered vitamin K has been widely publicized in the scientific journals and the medical colleges and its use has been adopted by all uptodate obstetricians and pediatricians. . . . If all expectant mothers were given vitamin K for a month before delivery and all babies were given a single dose of it immediately after their arrival, bleeding at birth would be reduced to a minimum—to those so badly injured that nothing can save them. This goal is indeed an inspiring one and the rank and file of American doctors can be trusted to attain it."

The evidence that vitamin K will prevent a prolongation of prothrombin time and will bring back to normal one that is already prolonged appears conclusive. This is the only claim that is made for it by the proponents of routine antenatal or neonatal administration. In order to determine whether routine administration to all patients is desirable, it becomes extremely important to

attempt to determine the incidence and mortality rate of hemorrhagic disease and of the number of hemorrhages that result in disability or death which are due to prothrombin deficiency.

Beck et al. gave 2 per cent as the incidence of hemorrhagic disease. According to Dam, "The percentage of babies with actual bleeding in the first week is about one per cent." Roberts stated that 0.7 per cent of the 19,052 infants in this series suffered from intracranial hemorrhage but considered this figure probably too low due to inadequacy of the data. Hellman et al. reported an incidence of 1:200 cases and included "hemorrhages, minute in brain, lungs, spleen, adrenal, thymus and liver," as well as cerebral hemorrhage, subcapsular hematomas of the liver, etc. Interestingly enough, in spite of the fact that the incidence of hemorrhagic disease was stated to be 0.5 per cent, Hellman believed he had reduced mortality from 4 per cent to 1.5 per cent, or five times the incidence of hemorrhagic disease, by giving vitamin K to prevent this condition. Waddell also reported 0.5 per cent and this figure is frequently quoted by other authors as the incidence of hemorrhagic disease.

In marked contrast to these figures is Sanford's statement that hemorrhagic disease, due to prolonged coagulation time, was found only twice among 5,500 babies.

Recent studies of infant mortality from several large obstetric hospitals give interesting figures. D'Esopo and Marchetti, at the Sloane Hospital for Women and the New York Lying-In Hospital, reported 21 fatal cases of hemorrhagic disease in 25,823 deliveries; Tyson at the Philadelphia Lying-in Hospital found hemorrhagic disease diagnosed as the cause of death in 8 of 15,488 deliveries. Clifford at the Boston Lying-In Hospital stated that fatal hemorrhagic disease occurred in 0.06 per cent of 31,786 deliveries, which would be about 19 cases. Potter from the Chicago Lying-in Hospital reported only 4 deaths due to hemorrhagic disease in 27,321 deliveries. This makes a total of 52 cases of fatal hemorrhagic disease in 100,378 deliveries, an incidence of approximately one in 2,000.

From the early papers following the discovery of vitamin K, it seemed that all infants with hemorrhagic disease suffered from prolonged prothrombin time, that this returned to normal following administration of vitamin K, and that the bleeding immediately ceased. Waddell and Guerry reported seven of eight infants with hemorrhagic disease cured by vitamin K, Kato and Poncher reported a cure in all of 22 cases, and Kato makes the statement: "Before the advent of specific therapy the mortality from hemorrhagic disease of the newborn has been estimated to have varied from 30 to 50 per cent; with the institution of vitamin K treatment the condition now need not be fatal." Waddell by personal contact with various investigators collected records of 4,141 infants treated with vitamin K prophylactically in which no case of hemorrhagic disease occurred.

Only a few investigators have questioned the efficacy of vitamin K in stopping or preventing hemorrhage. Parmalee has reported two cases of severe melena associated with marked prolongation of prothrombin time, in which the bleeding did not stop following vitamin K administration in spite of the fact that the prothrombin time returned to normal very promptly. Scobbie failed to find the prothrombin time prolonged in all of 15 cases of hemorrhagic disease in which it was determined, and stressed the fact that many infants without hemorrhage exhibited prothrombin times as prolonged as those with severe hemorrhage.

Ponches stated: "Vitamin K prophylaxis with the correction of the hypoprothrombinemic state is only one phase in the management of hemorrhage in the newborn period and is not a substitute for good obstetrical care and the prevention or prompt recognition and treatment of the other factors." Kove and Siegel, Capon, Snelling, and other investigators have commented that some additional factor is necessary before a prolonged prothrombin time will produce hemorrhage.

When Sanford and his co-workers published their study of vitamin K in relation to the occurrence of hemorrhage, their conclusion that the administration of vitamin K had not modified the incidence of hemorrhagic manifestations was met with a storm of comment. They reported an equal incidence of gastrointestinal, vaginal, umbilical, dermal, cerebral, and subepicranial hemorrhages in a group of 711 newborn infants given vitamin K by mouth immediately after birth, and in 782 who were not given the vitamin. The mortality was the same in the two groups. They felt that conditions other than vitamin K deficiency were probably responsible for the majority of hemorrhagic manifestations in the newborn infant, and that infants should not be included in the category of hemorrhagic disease simply because they had some evidence of bleeding.

They state: "In the reports of hemorrhagic disease during the newborn period that have been published recently it is apparent that all of these hemorrhagic manifestations have

been lumped into the one term "hemorrhagic disease of the newborn), which, it is assumed, is due to a deficiency of prothrombin. We have been unable to show that these hemorrhagic manifestations were associated with a prothrombin deficiency, nor were they lessened by the administration of vitamin K." They believed no baby in their series had hemorrhagic disease, and although they showed definitely that administration of vitamin K will shorten the prothrombin time and is consequently of value in the treatment of any condition due to a prolongation, they concluded that, except in true hemorrhagic disease, administration of the vitamin is without value. The incidence of hemorrhagic disease in their experience was 1:2,500 births.

Immediately after the publication of this article, Quick, in a communication to the *Journal of the American Medical Association*, said: "If the aim of Dr. Sanford and his associates is to emphasize that hemorrhages in the newborn can occur from causes other than prothrombin deficiency, they are serving a laudable purpose; but on the other hand if they are attempting to depreciate the value of vitamin K in preventing and curing the hemorrhagic disease of the newborn, one is forced for the sake of the newborn baby to take sharp issue with them."

It would appear that Dr. Sanford had not been depreciating the value of vitamin K in the treatment of hemorrhagic disease, but had been definitely questioning whether the incidence of true hemorrhagic disease was sufficient to warrant the administration of the drug to very large numbers of patients in order to prevent the disease in a very few.

A few weeks later Waddell, also in a communication to the *Journal of the American Medical Association*, stated that he was "forced to join with Dr. Quick in taking prompt and sharp exception to Dr. Sanford's conclusions." He quotes the work of Beck et al., and Hellman et al., giving conclusive proof that mortality rates can be greatly decreased and the incidence of hemorrhage reduced by the prophylactic administration of vitamin K to the mother prior to delivery, and adds, somewhat ambiguously, "we have also repeatedly expressed the hope, adequately supported by facts, that infant mortality resulting from intracranial hemorrhage will in the future possibly be materially reduced by this sound therapeutic procedure." Among his own patients he gives the amazingly high incidence of 10.4 per cent with hemorrhage in a control group of infants and 1.07 per cent in another group, the difference supposedly being due to the use of vitamin K.

Kugelmass, also commenting on Sanford's paper, stated that hemorrhagic disease of the newborn is a disease entity due specifically to prothrombin deficiency and that "since the disease occurs in less than 0.5 per cent of all newborn infants it is folly to waste vitamin K on 99.5 per cent of the remainder even if many of these may show hemorrhagic manifestations! If the latent hemorrhagic tendency present in all newborn infants becomes active, the rise in clotting time will indicate decrease in available prothrombin. Then, and only then is vitamin K therapy indicated." His incidence of hemorrhagic disease is 12.5 times that given by Sanford but there is no comment as to the source of the data, and in spite of this greater frequency he still does not believe routine administration of vitamin K justified.

According to Dam, Sanford's view "is in fact difficult to understand since sufficiently lowered prothrombin time always will lead to bleeding." Dam's statement, however, does not reflect the general opinion of most investigators.

An editorial in the English publication, *Lancet*, commended Sanford's paper for throwing scientific doubt "on what was becoming too simple—low prothrombin, hemorrhagic disease, vitamin K, cure," and concluded that "it is palpably absurd to lump all hemorrhagic manifestations of the newborn together and pretend that this is hemorrhagic disease due to prothrombin deficiency and preventable and curable by giving vitamin K."

After reading the editorial on Sanford's paper, Capon agreed that the paper gave welcome support against the idea of many recent investigators that hemorrhagic disease includes all types of hemorrhage, and said, "There is some additional factor with low prothrombin of the blood causing hemorrhagic disease of the newborn infant."

MacPherson and Henderson, in response to the same editorial, thought that one could relegate to the "proper station such minor accidents as Sanford describes" but that this still did not depreciate the routine use of vitamin K as a preventive or cure of hemorrhagic disease.

Parks and Sweet, in an attempt to find further evidence as to the validity of the statement that vitamin K could be expected to reduce materially the number of infants with hemorrhage and to decrease total death rates, gave 5 mg. vitamin K orally on admission to the hospital to 1,151 women, alternating them with 1,594 who received no vitamin K. They found abnormal bleeding in 1.7 per cent of the infants born to the first group of mothers

and in 1.4 per cent of the second group. The mortality among infants weighing over 1,000 grams alive on admission and dying within two weeks, whose mothers received vitamin K, was 4.1 per cent; for those whose mothers were untreated, 4.9 per cent. Hemorrhage not definitely due to trauma was associated with 10 per cent of deaths in both groups. The vitamin K was effective in raising the blood prothrombin levels of both mothers and infants. They say, "If an elevated prothrombin level is a significant factor in preventing neonatal hemorrhage we are unable to explain the results of our clinical survey." This paper, although appearing at about the same time as the one by Sanford et al. and in fundamental agreement with it, seems to have received little attention.

It is the paper of Beck and his co-workers and the work of Hellman and his associates that are most constantly referred to as giving proof of the efficacy of vitamin K in materially lowering the incidence of hemorrhage, and consequently in lowering infant death rates.

Beck et al. alternated cases and gave vitamin K to 1,022 mothers; among their infants 4 appeared to have suffered intracranial hemorrhage, one had bloody stools. The mothers of 1,037 infants received no vitamin K; in this group there were 14 infants with a diagnosis of intracranial hemorrhage and 7 with bloody stools. This is an apparent reduction in the incidence of hemorrhage from 2 to 0.5 per cent. There is no mention of how the diagnosis of intracranial hemorrhage was made nor of the mortality rate, and Beck, in closing the discussion on the paper, stated in regard to the infants with bloody stools, "These were not typical cases of melena neonatorum but in all of them a diagnosis of bleeding of some character was made." The incidence of 2 per cent with hemorrhage which was found in the control series is much higher than that reported by almost any other clinic.

Hellman, Shettles, and Eastman, in 1940, reported a mortality of 4.1 per cent among the infants of 384 women who had had vitamin K prior to delivery and only 1.5 per cent among 392 without vitamin K. They state that this is a statistically significant difference, and yet it is not a sufficiently large series on which to base an opinion, for it is the experience of practically every clinic delivering large numbers of babies that many hundreds may be born with almost no mortality, only to be followed by a compensatory increase a short time later.

Realizing this fact, Hellman and Shettles subsequently reported over 1,000 infants whose mothers had had vitamin K and approximately an equal number whose mothers had not been given the vitamin. The incidence of prematurity was almost twice as great and of cesarean section almost four times as great in the control as in the treated cases. The uncorrected mortality was given as 3.9 per cent and 1.9 per cent and the statement was made that, since the mortality following cesarean section was 12 per cent in each series, the variation in the number in the two series can be disregarded. However, the difference between 12 per cent of 100 cesarean sections and 12 per cent of 26 cesarean sections immediately weights the untreated series by adding 9 deaths to that group. The authors stated that, in removing all deaths of premautres or following cesarean sections, the mortality was 1.2 in the treated and 2.4 in the untreated. If the figures are recalculated, however, it seems probable that only the premature infants were removed. If cesarean sections are also eliminated, the mortality becomes 0.9 in the treated and 1.5 in the untreated, a difference less impressive than between 3.9 and 1.9 per cent. In small groups of 1,000 cases each, a difference between 9 deaths and 15 deaths can be due to chance.

In order to further evaluate the claims made by various investigators that vitamin K if administered to all pregnant women during labor would reduce neonatal mortality rates by decreasing the number of infants who die of hemorrhage, a study of this subject was initiated at the Chicago Lying-in Hospital. Most previous investigations have included a very small group of patients or the vitamin has been given to alternate women. In order to overcome the inaccuracies inherent in inadequate data, and the selection which is inevitable when an attempt is made to alternate patients, it was decided to give vitamin K to all women delivered during a two-year period, to stop this medication and to use the following two years for a control. The vitamin in the form of 3.2 mg. Hykinone (2-methyl-1, 4-naphthohydroquinone-3-sodium sulfonate)* was given

*The author is grateful to the Abbott Laboratories for supplying the Hykinone used in this entire study.

to all patients on admission to the labor rooms. The parenteral route was chosen in order to prevent loss by emesis.

Personal Observations

From Jan. 1, 1941, until Nov. 1, 1944, 13,190 infants weighing over 1,000 grams were born in this hospital. Among 6,502 mothers delivered during the first two years, 6,004 received vitamin K. The reasons for failure to administer it to 498 included too short an interval between admission and delivery, antepartum death of the fetus, nonavailability of the vitamin. Of the 6,004 patients who received vitamin K, the exact interval between the administration of K and delivery was recorded in 5,833. Almost half of the patients (45.53 per cent) received it more than one but less than six hours prior to delivery. In 7.46 per cent the interval was less than one hour; it was more than six and less than twelve in 25.04 per cent; from twelve to eighteen in 11.3 per cent; eighteen to twenty-four in 6.0 per cent and over twenty-four in 4.6 per cent.

A total of 6,560 infants were born; of these 89 died within ten days of birth, and 108 were dead at the time of delivery. This is a neonatal mortality of 13.4 per 1,000 births and a stillbirth rate of 16.4, making a total fetal and infant mortality of 29.8 per thousand births.

On Jan. 1, 1943, the administration of the vitamin was discontinued, and from then until Nov. 1, 1944, a total of 6,630 infants were delivered. Among these, 82 were stillborn and 90 who were born alive failed to survive for ten days. This gives a neonatal mortality rate of 13.5 and a stillbirth rate of 12.3 or a combined rate of 25.8 per 1,000 births.

During 1941 and 1942, the vitamin was given to a few babies after birth whose mothers had failed to receive it during labor. During the following two years it was also occasionally administered, particularly to very premature babies, but fewer than 100 received it. It was given empirically because of the possibility that it might increase the chances of survival, and only rarely because of visible bleeding.

Examination of the death rates for the two years during which vitamin K was given and for the following two years show almost identical rates for the first ten days of life, and a distinctly lower stillbirth rate in the control series. It might be argued that other more favorable conditions existed during 1943-1944 which offset any loss of life occasioned by the failure to administer vitamin K. During the latter years the proportion of multiparous patients was slightly greater than in the previous years but, as shown in Table I, the total mortality rates decreased in both multiparous and primiparous patients and in both years the rate for multiparars is greater than for primiparas. If the rates for 1943-1944 were to show any change because of the increase in the number of multiparas, it should be in the direction of increased mortality.

The incidence of prematurity (weight from 1,000 to 2,500 grams) among liveborn infants is slightly less (Table II) in 1943-1944 (6.5 per cent) than in the previous years (7.1 per cent) but the difference is only 0.6 per cent and is not statistically significant. The premature mortality rate is 12 per cent in both periods. Mortality for infants born alive at term (over 2,500 grams) is 0.5 per cent in both periods.

The incidence of various methods of delivery shows little variation in 1941-1942 and 1943-1944 (Table III). Low and outlet forceps were used slightly more frequently during 1943-1944 and natural cephalic deliveries were com-

TABLE I. MORTALITY RATES IN RELATION TO MATERNAL PARITY

	TOTAL BIRTHS	DEATHS		STILLBIRTHS		DEATHS AND STILLBIRTHS PER 1,000 BIRTHS
		NUMBER	PER 1,000 BIRTHS	NUMBER	PER 1,000 BIRTHS	
1941-1942 (Vitamin K)						
Primiparas	3,130	36	11	56	17	28
Multiparas	3,430	53	15	52	15	30
1943-1944 (No Vitamin K)						
Primiparas	2,692	34	13	30	11	24
Multiparas	3,938	55	13	52	13	26

TABLE II. RELATION OF PREMATURITY TO MORTALITY

	BIRTHS		DEATHS		STILLBIRTHS	
	(NO.)	(%)	(NO.)	(%)	(NO.)	(%)
1941-1942 Vitamin K						
Term	6,092	92.9	31	0.5	53	0.9
Premature	468	7.1	58	12.4	55	11.7
Total	6,560	100.0	89	1.3	108	1.6
1943-1944 No Vitamin K						
Term	6,198	93.5	34	0.5	43	0.7
Premature	432	6.5	56	12.9	39	9.0
Total	6,630	100.0	90	1.3	82	1.2

TABLE III. METHOD OF DELIVERY IN VITAMIN K AND CONTROL SERIES

	VITAMIN K 1941-1942	NO VITAMIN K 1943-1944
Total infants	6,560	6,630
Natural cephalic	50.7%	44.7%
Low forceps	37.2	43.3
Midforceps	2.9	2.6
Version and extraction	0.7	0.6
Breech	4.1	4.1
Cesarean	4.0	4.4
Other	0.4	0.3
Total	100.0%	100.0%

pensatorily decreased. Although total mortality is somewhat greater in natural cephalic deliveries than when low forceps are used, this is because the majority of macerated and malformed fetuses are delivered without operative interference. When fetuses dead before the onset of labor and those suffering from malformations or erythroblastosis are deleted, the mortality rates associated with the two types of delivery are practically identical. It is evident, therefore, that manner of delivery has not affected mortality rates in these two periods.

Of the 369 infants who were born dead or died during the four years, 334 were subjected to postmortem examination. The causes of death are shown in Tables IV and V. The pathologic lesions found in the infants who were born alive show remarkable similarity in the period when vitamin K was given and when it was discontinued. Each group has approximately the same number of infants with hemorrhagic manifestations, and associated with practically all of these there were abnormalities of labor or delivery which appeared to be definite causative factors. Placenta previa, premature detachment of the placenta, or cord prolapse were the cause of the anoxia which caused petechial hemorrhages in eleven infants, and were also present in the majority of infants with pulmonary hemorrhage. Intracranial hemorrhage was almost always associated with definite trauma incurred during labor or delivery.

TABLE IV. STILLBIRTHS IN VITAMIN K AND CONTROL SERIES

	VITAMIN K 1941-1942		NO VITAMIN K 1943-1944	
Total births	6,560		6,630	
Malformation	13		6	
Erythroblastosis	6		9	
Pneumonia	7		0	
Syphilis	1		1	
Abdominal pregnancy	2		0	
No abnormalities	48		36	
Antepartum				
Toxemia	11		6	
Nontoxic	35		27	
Intrapartum				
Nontoxic	2		3	
		77		52
Anoxia (petechial hemorrhages)		27		26
abruptio	8		13	
cord prolapse or knot	11		6	
uterine abnormality	4		4	
placenta previa	4		3	
Intracranial hemorrhage		4		3
Liver hemorrhage		0		1
		31		30
Total		108		82
Stillbirth rate per 1,000 births		16.4		12.3

TABLE V. NEONATAL DEATHS IN THE VITAMIN K AND CONTROL SERIES

	VITAMIN K 1941-1942	NO VITAMIN K 1943-1944
Total births	6,560	6,630
Prematurity (no abnormalities)	27	26
Malformation	18	23
Erythroblastosis	7	12
Pneumonia	12	7
Edema of meninges	4	2
Miscellaneous	2	2
Unknown	1	3
	71	75
Anoxia (petechial hemorrhages)	6	5
Intracranial hemorrhage	9	5
Pulmonary hemorrhage	2	5
Hemorrhagic disease (?)	1	1
	18	16
Total	89	91
Death rate per 1,000 births	13.5	13.5

In only two infants did the possibility of true hemorrhagic disease exist, and in neither of these is the diagnosis conclusive. One 3,100-gram male infant, the child of a 22-year-old primigravida, was delivered naturally from a cephalic position after a labor of 7 hours and 13 minutes. Hykinone (3.2 mg.) was given 2 hours and 10 minutes before delivery. Heart tones had been irregular during the latter part of labor and meconium was evacuated into the amniotic fluid. Respiration was delayed for several minutes after birth and when finally initiated remained irregular and grunting in character. The infant was placed in a Hess bed, given oxygen and respiratory stimulants, but continued to do poorly and died after 29 hours and 30 minutes. Autopsy examination disclosed multiple perforations of the stomach with a large amount of blood in the stomach and in the peritoneal cavity, a small hemorrhage in the right adrenal gland, and early pneumonia, together with large numbers of epithelial cells from the amniotic fluid in the pulmonary alveoli.

The second infant was born in June, 1944. It was a female, weighed 3,795 grams, and was delivered by low forceps after an uneventful labor of 15 hours, 10 minutes. The mother

was a 24-year-old primipara. Respiration was extremely delayed and intratracheal oxygen was given for twenty minutes before breathing began. The infant was placed in a Hess bed and continued to do poorly. It was cyanotic, breathed irregularly, and did not move unless stimulated. It was given 3.2 mg. Hykinone one hour after birth, together with coramine and caffeine. At 6 hours of age it vomited a small amount of blood and had bloody stools; a second dose of vitamin K was given at this time. The infant continued to do poorly, and 60 c.c. of blood were given intravenously at 18 hours. There was little response and the infant succumbed at the age of 50 hours. Autopsy examination revealed a spectacular picture of hemorrhage and infarction of liver, spleen, kidneys, lungs, and adrenal glands. There was also free blood in the intestine. The brain and cranial cavity were normal. Blood smears made on the first day of life showed no evidence of platelets, and subsequently it was learned that the mother of the infant was very subject to skin petechiae, that her maternal grandfather was a "bleeder," that a maternal aunt died at 18 months of multiple hemorrhages, and that her mother had an unusual tendency to bleed. Whether this should be considered hemorrhagic disease, whether it is entirely the result of anoxia, or whether it is some type of familial purpura cannot be determined.

If these are cases of hemorrhagic disease, they are instances of a failure to respond to vitamin K. If they are not hemorrhagic disease, it means that, in over 13,000 infants, none has died of hemorrhagic disease.

The stillbirth rate was 4 per thousand less during 1943-1944 than during the time when vitamin K was given. This saving has been almost entirely in deaths which could in no way be related to prothrombin time. The incidence of any type of hemorrhage is practically the same in the two groups, and in these, as in the neonatal deaths, there is no evidence that anything beyond trauma or interference with oxygenation of the fetal blood was a causative factor.

From a study of this material it seems justifiable to conclude that the routine administration of vitamin K during labor in no way affected the infant mortality or stillbirth rate in the Chicago Lying-in Hospital. The mortality rates for liveborn infants of 13.5 (1941-1942) and 13.5 (1943-1944) and the stillbirth rates of 16.4 (1941-1942) and 12.3 (1943-1944) per 1,000 births compare very favorably with mortality rates reported from any obstetric hospital. The mortality rates are as low as any which to my knowledge have been reported from a large maternity service.

The question is raised as to the validity of a diagnosis of hemorrhagic disease unrelated to trauma, anoxia, or some other pathologic state. Clifford stated that 50 per cent of his 69 infants with hemorrhagic disease were sufficiently asphyxiated to require artificial resuscitation, and among the cases of authors who stress the importance of hemorrhagic disease as a cause of death the incidence of intracranial hemorrhage is always high.

According to Waddell, "Obstetric trauma in some instances is the precipitating factor in intracranial hemorrhage, thus initiating hemorrhage in an infant that is by reason of prothrombin deficiency a potential bleeder." It is the feeling in the Chicago Lying-in Hospital that the incidence of intracranial hemorrhage is directly related to the skill and judgment of the obstetrician, and that instead of being a common cause of death it should be low, and become constantly lower. Whether it is justifiable to accept the concept of hemorrhagic disease as an entity entirely unrelated to some inciting factor other than a prolongation of prothrombin time seems open to question.

It is possible that the few infants who received vitamin K during 1943-1944 may have been benefited. As stated before, it was given because it was known to be harmless and because it might possibly do some good. In no case was a diagnosis of hemorrhagic disease made (except possibly the two fatalities previously mentioned) and at no time in the past four years has any infant (except one of these fatal cases) been transfused for loss of blood by hemorrhage.

Conclusion

Evidence has been produced by many investigators which leaves no doubt (1) that in the majority of infants the prothrombin time is prolonged during the greater part of the first week of life beyond that which is normal for the adult, (2) that the administration of vitamin K to the mother prior to delivery or to the infant after birth will usually prevent the customary prolongation, (3) that after prolongation has once occurred, administration of vitamin K will usually cause a return to normal.

There is no proof, however, that prolongation of prothrombin time is a direct cause of hemorrhage. Many infants with excessively prolonged prothrombin time show no evidence of hemorrhage, while others with relatively little prolongation bleed severely. Since almost all infants show some prolongation of prothrombin time during the first week, all who bleed from any cause would be expected to show some abnormality.

The optimistic propheeies which were made early in the study of vitamin K in regard to prevention of hemorrhage and reduction in mortality rates following routine administration of vitamin K do not seem to have materialized. The present study, as well as the investigations of Sanford et al. and Parks and Sweet, indicate that in a carefully studied group of infants anything which can be considered hemorrhagic disease is extremely rare, and that the incidence of the hemorrhages which do occur in this age group is not modified by administration of vitamin K to the mother prior to delivery, or to the infant after birth.

In the present study, which was carried on for almost four years, 6,560 infants weighing over 1,000 grams were born during the two years in which vitamin K was given, and 6,630 were born during the next twenty-two months. The total fetal and infant mortality rate of 29.8 for the first two years is higher than that of 25.8 for the last two years in spite of the fact that no change of significance occurred in the incidence of primiparity, premature delivery, mode of delivery, or other known factor. The mortality rates for liveborn infants are identical in the two series, as are also the numbers of infants who showed evidence of hemorrhage on postmortem examination.

The conclusion seems justified that no decrease in infant or fetal mortality can be expected to result from the routine administration of vitamin K to all women during labor.

References

1. Ballon, O.: Schweiz. med. Wchnschr. **72**: 1119, 1942. (Abst., Greenhill, Am. J. Obst. & Gynec. **46**: 908, 1943.)
2. Beck, A. C., Taylor, S., and Colburn, R. F.: Am. J. Obst. & Gynec. **41**: 465, 1941.
3. Bohlender, G. P., Rosenbaum, W. M., and Sage, E. C.: J. A. M. A. **116**: 1763, 1941.
4. Brinkhous, K. M., Smith, H. P., and Warner, E. D.: Am. J. M. Sc. **193**: 475, 1937.
5. Bruchsaler, F. S.: J. Pediat. **18**: 317, 1941.
6. Capon, N. B.: Lancet **2**: 887, 1932.
7. Capon, N. B.: Lancet **1**: 602, 1942.
8. Clifford, S. H.: J. Pediat. **8**: 367, 1936.
9. Clifford, S. H.: J. Pediat. **14**: 333, 1939.
10. Clifford, S. H.: J. Pediat. **20**: 650, 1942.
11. Dam, H.: Journal-Lancet **63**: 353, 1943.
12. Editorial: Lancet **1**: 481, 1942.
13. D'Esopo, D. A., and Marchetti, A. A.: Am. J. Obst. & Gynec. **44**: 1, 1942.
14. Fiechter, N.: Schweiz. med. Wchnschr. **72**: 1252, 1942. (Abst., Greenhill, Am. J. Obst. & Gynec. **46**: 907, 1943.)
15. Fitzgerald, J. E., and Webster, A.: Am. J. Obst. & Gynec. **40**: 413, 1940.
16. Fitzgerald, J. E., and Webster, A.: J. A. M. A. **119**: 1082, 1942.
17. Gellis, S. S., and Lyon, R. A.: J. Pediat. **19**: 495, 1941.
18. Grossman, A. M.: J. Pediat. **19**: 205, 1941.
19. Hardwicke, S. H.: J. Pediat. **24**: 259, 1944.
20. Hellman, L. M., and Shettles, L. B.: South. M. J. **35**: 289, 1942.

21. Hellman, L. M., and Shettles, L. B.: Bull. Johns Hopkins Hosp. **65**: 138, 1939.
22. Hellman, L. M., Shettles, L. B., and Eastman, N. J.: Am. J. Obst. & Gynec. **40**: 844, 1940.
23. Huber, C. P., and Shrader, J. C.: Am. J. Obst. & Gynec. **41**: 566, 1941.
24. Javert, C. T.: Am. J. Obst. & Gynec. **40**: 453, 1940.
25. Javert, C. T., and Moore, R. A.: Am. J. Obst. & Gynec. **40**: 1022, 1940.
26. Kato, K.: Clinics **2**: 33, 1943.
27. Kato, K., and Poncher, H. G.: J. A. M. A. **114**: 749, 1940.
28. Kove, S., and Siegel, H.: J. Pediat. **17**: 448, 1940.
29. Kove, S., and Siegel, H.: J. Pediat. **18**: 764, 1941.
30. Kove, S., and Siegel, H.: J. Pediat. **19**: 503, 1942.
31. Kugelmass, I. N.: J. A. M. A. **118**: 1389, 1942.
32. Lawson, R. B.: J. Pediat. **18**: 224, 1941.
33. Lehmann, J.: Lancet **1**: 493, 1944.
34. MacPherson, A. I. S., and Henderson, J. L.: Lancet **1**: 546, 1942.
35. Mathews, G. O.: Bull. Vancouver M. A. **18**: 342, 1942.
36. McReady, L. L., Callahan, E. T., and Grandin, D. J.: Am. J. Obst. & Gynec. **42**: 398, 1941.
37. Mull, J. W., Bill, A. H., and Skowronska, H.: J. Lab. & Clin. Med. **26**: 1305, 1941.
38. Nygaard, K. K.: Acta obst. et gynec. Scandinav. **19**: 247, 1939.
39. Owen, C. A., Hoffman, G. R., Ziffren, S. E., and Smith, H. P.: Proc. Soc. Exper. Biol. & Med. **41**: 181, 1939.
40. Parmalee, A. H.: J. Michigan M. Soc. **42**: 455, 1943.
41. Parks, J., and Sweet, L. K.: Am. J. Obst. & Gynec. **44**: 432, 1942.
42. Poncher, H. G.: Advances in Pediat. **1**: 151, 1942.
43. Poncher, H. G.: J. Pediat. **20**: 637, 1942.
44. Poncher, H. G., and Kato, K.: J. A. M. A. **115**: 14, 1940.
45. Portes, L., and Varangot, J.: Presse méd. **49**: 812, 1941.
46. Potter, E. L.: Am. J. Obst. & Gynec. **45**: 1054, 1942.
47. Quick, A. J.: Wisconsin M. J. **38**: 746, 1939.
48. Quick, A. J.: J. A. M. A. **118**: 999, 1942.
49. Quick, A. J., and Grossman, A. M.: Proc. Soc. Exper. Biol. & Med. **40**: 647, 1939; **41**: 227, 1939.
50. Quick, A. J., and Grossman, A. M.: Am. J. M. Sc. **199**: 1, 1940.
51. Richardson, F. H.: Hygeia **21**: 254, 1943.
52. Richdorf, L. F., and Kearney, W.: Journal-Lancet **62**: 155, 1942.
53. Roberts, M. H.: J. A. M. A. **113**: 281, 1939.
54. Rodda, F. C.: J. A. M. A. **75**: 452, 1920.
55. Russell, H. K., and Page, R. C.: Am. J. M. Sc. **202**: 355, 1941.
56. Sage, E. C.: Nebraska M. J. **27**: 314, 1942.
57. Salomonsen, L., and Nygaard, K. K.: Acta paediat. **27**: 209, 1939.
58. Sanford, H. N., Morrison, H. J., and Wyat, L.: Am. J. Dis. Child. **43**: 569, 1932.
59. Sanford, H. N., and Leslie, E. I.: J. Pediat. **12**: 16, 1938.
60. Sanford, H. N., Shmigelsky, I., and Chapin, J. M.: J. A. M. A. **118**: 697, 1942.
61. Scobbie, E.: Arch. Dis. Childhood **17**: 175, 1942.
62. Shettles, L. B., Delfs, E., and Hellman, L. M.: Bull. Johns Hopkins Hosp. **65**: 419, 1939.
63. Snelling, C. E.: J. Pediat. **17**: 615, 1940.
64. Snelling, C. E., and Nelson, W.: J. Pediat. **17**: 615, 1940.
65. Snelling, C. E., and Nelson, W.: J. Pediat. **22**: 77, 1943.
66. Toohey, M.: Arch. Dis. Childhood **17**: 187, 1942.
67. Townsend, C. W.: Arch. Pediat. **11**: 559, 1894.
68. Tyson, R. M.: Am. J. Obst. & Gynec. **37**: 241, 1939.
69. Valentine, E. H., Reinhold, J. G., and Schneider, E.: Am. J. M. Sc. **202**: 359, 1941.
70. Vollmer, H., Adler, C., and Altman, H. S.: Am. J. Dis. Childhood **64**: 462, 1942.
71. Waddell, W. W.: J. Pediat. **20**: 656, 1942.
72. Waddell, W. W.: J. A. M. A. **118**: 1389, 1942.
73. Waddell, W. W., and Guerry, Du P., III: J. A. M. A. **112**: 2259, 1939.
74. Waddell, W. W., and Lawson, G. M.: J. A. M. A. **115**: 1416, 1940.
75. Warner, E. D.: M. Clin. North America **27**: 371, 1943.
76. Webster, A., and Fitzgerald, J. E.: S. Clin. North America **23**: 85, 1943.
77. Willumsen, H. C., Stadler, H. E., and Owen, C. A.: Proc. Soc. Exper. Biol. & Med. **47**: 116, 1941.

THE CONSERVATIVE MANAGEMENT OF SOME VARIETIES OF PLACENTA PREVIA*

HERMAN W. JOHNSON, M.D., F.A.C.S., HOUSTON, TEXAS

(From the Department of Obstetrics, Baylor University College of Medicine, and the Maternity Division of St. Joseph's Infirmary)

THE main purpose of this paper is an attempt to drive away some of the goblins which have long, long ago been drawn into the picture of placenta previa and have been handed down from one edition to the next edition of acceptable textbooks on obstetrics with no evidence of revision commensurate with increased clinical experience. A second purpose is to urge most conservative measures when the decision is made to effect delivery per vaginam.

Vigorous protest should be made against continuously inculcating into the minds of medical students and of practicing physicians the impression that a case of placenta previa can end fatally as a direct result of the first blood loss, or even of any subsequent bout of bleeding, when no attempt at delivery has been made.

The following quotations from obstetric textbooks in common usage today exemplify the outmoded statements referred to above. Stander-Williams,[1] "Ordinarily the initial bleeding is rarely so profuse as to prove fatal, and ceases spontaneously, to recur again when least expected. . . . In a certain proportion of cases, particularly when the insertion is marginal, the bleeding does not appear until the time of labor, when it may vary from a slight bloodstained discharge to a profuse or even fatal hemorrhage." DeLee-Greenhill,[2] "The first hemorrhage may vary from a few drops, hardly a stain on the linen, to a profuse 'flooding,' which may be fatal at once, but usually a few ounces are lost as the initial symptom." Beck,[3] "The initial loss of blood is quite profuse and often alarming. Fortunately, however, it seldom is fatal."

The inference from these acceptable authors is that the spontaneous bleeding from placenta previa sometimes is fatal. It is the author's opinion that the obstetrician should not approach or behold a case of placenta previa with this unwarranted fear in his mind, since such an attitude might cause him to resort to measures in treatment which might be too drastic or untimely. Furthermore, these same authors importune the physician to terminate the pregnancy as soon as the diagnosis of placenta previa has been made. This appears unwarranted. There would seem to be no good reason for sacrificing the life of a fetus merely because its placenta happened to be implanted over or near the cervical os. More particularly is this true when the claimed serious threat to the life of the mother is still unproved. The high fetal mortality in placenta previa cannot be reduced unless the pregnancy is allowed to proceed into the period of viability and until the practice of using the body of the fetus as a mechanical tampon is discontinued.

It is essential to proper treatment that all means at our command be used for the purpose of making a correct diagnosis. The assumption that vaginal bleeding at term or during the last trimester is due to placenta previa is grossly erroneous. Moreover, it should be constantly borne in mind that only about 33 per cent of such cases of bleeding are actually due to placenta previa.

*Read before the Fifteenth Annual Meeting of the Texas Association of Obstetricians and Gynecologists, Nov. 22, 1944, Dallas, Texas.

Further evidence in support of the low incidence of placenta previa in cases presenting varying amounts of vaginal bleeding is found in the following quotation from a statistical report by Dippel and Brown,[4] "As a matter of fact, there were only eleven instances of clinical placenta previa in the group, while the remaining fifteen were merely roentgenologic instances of low implantation of the placenta. There were only two cases where clinical evidence of premature separation of the normally implanted placenta was present. Therefore, if cesarean section had been routinely performed on all cases of vaginal bleeding on the assumption that they had either placenta previa or premature separation of the placenta, that assumption would have been erroneous, and cesarean section would have been unjustifiably performed in 85.87 per cent of the cases."

For obstetricians it might be well to reverse the dictum which ends". . . is due to placenta previa unless proven otherwise," to ". . . is due to other causes unless proven placenta previa." This suggested change does not mean that the obstetrician should become less insistent upon making an accurate diagnosis in all cases of vaginal bleeding.

Two methods of localizing the placenta are available, namely, x-ray visualization and manual examination. All cases of suspected placenta previa should have the benefit of both. Needless to say, the element of error will be decreased with the skill of those making the examinations. The great advantage of roentgen localization of the placenta has been amply shown by Dippel and Brown.[4] They were able to visualize the placenta 236 times out of 262 observations, an incidence of 90 per cent. Unfortunately, the assistance of skilled observers in placental visualization is not generally available and unskilled interpretations are dangerous. A reliable interpretation, when available, serves as a check on the vaginal examination, i.e., it is further proof of where the placenta is or is not.

It is the author's opinion that a sterile vaginal examination is essential for accurate diagnosis. This should be done in all suspected cases and done whether there is bleeding or not. Rectal examinations are contraindicated, as zeal for information may cause too much trauma. Naturally, the vaginal examination should be done with due consideration for the exigencies of the case, and with extra precaution against infection. As for preparedness for delivery or transfusion at the time of this examination, more will be said later.

The vaginal examination means nothing to fingers that have not palpated hundreds of perfectly normal cases late in pregnancy and in labor, because only normal findings can be used to evaluate departures from the normal. The trained finger knows the usual station of the head, the usual station of the body of the cervix; and if not in labor, the degree of ripening of the cervix and the location of its internal os. If in labor, the amount of effacement or dilatation is known. The trained examiner knows that the lower uterine segment is very thin and through it the presenting pole may be easily palpated for some distance lateral, as well as posterior and anterior to the cervical os. Normally, throughout this area nothing save varying quantities of amniotic fluid is interposed between the fingers and the presenting pole. If a mass is interposed, however, its thickness, extent, and location will be of great significance. Thus, without even invading the cervix, it may be possible to make a reasonably accurate diagnosis of the various degrees of placenta previa from low implantation of the placenta to placenta previa centralis. On the other hand, in multiparas in labor, with effacement of the canal and some dilatation of the external os, the finger may be gently inserted in quest of a place where only membranes are felt and for the purpose of rupturing them. If one is fortunate enough to have x-ray interpretations and a careful vaginal exami-

nation to fit into the clinical picture, the percentage of error in the diagnosis of placenta previa should be very small.

Some apology should be made for reciting so much elementary obstetrics, but it has occurred to me many times that the books have not laid enough stress on normal findings in the differential diagnosis of abnormal conditions.

The forces of labor are not altered in placenta previa; therefore, in the nontoxic cases (the combination of previa and toxemia is extremely rare) there would be no reason to suspect any difference in the process of effacement, dilatation, placental separation and expulsion, except that as dilatation progresses, uteroplacental sinuses are abrupted and this is accompanied by intermittent bleeding.

The amount of bleeding at any given time is largely dependent on the amount of dilatation occurring at that moment, since it is the cervical dilatation that causes the abruption. This is not true of the centralis variety. When the hemorrhage is profuse, with little or no dilatation, one may be reasonably certain that he is dealing with a case of the central type.

Fortunately, the time required to complete the first stage of labor is at least four hours. The bleeding is intermittent and, as mentioned, is caused by the periods of dilatation and not directly by the labor pains. The foregoing statement might be open to question, but everyone who has observed dilatation carefully must feel that the progress of dilatation varies in every labor and in different periods in each labor. These periods of progress seem not to take place with each pain but, when they occur, represent the accumulative effect of many pains. Fibroelastic tissue may require a process of softening between each period of dilatation. Perhaps this mechanism is a lifesaver in placenta previa, because it permits nonbleeding periods, i.e., periods which allow the patient to regain some blood volume. If the foregoing concept of the mechanics of separation in placenta previa is true, it permits of two reasonable conclusions: first, that a careful vaginal examination cannot simulate a series of labor pains building up to a period of dilatation and separation with hemorrhage. The examination may be coincidental with the period of dilatation and bleeding, but not the cause. This may be easily proved by making another examination immediately following the cessation of the current bleeding. Second, a patient at or near term going into labor might require four hours or more to complete the first stage. If she lost 1,500 c.c. during this entire period, it would mean a steady blood loss of 6 c.c. per minute, but if the loss were at intervals of ten minutes, the periodic amount lost would be 60 c.c. This long range intermittent loss of blood with its opportunities for natural and for transfusion replacement could hardly prove lethal. Therefore, the conclusion seems reasonable that there is little danger of the patient's bleeding to death, provided active measures to effect delivery of the baby or placenta are not taken.

The fetal mortality in placenta previa will always be high. Naturally, it would be expected to be lowest in deliveries effected by cesarean section; but even here we should be reluctant to promise the family a living and well baby. The incidence of fetal abnormalities associated with placenta previa, as shown by Greenhill,[5] is considerable. In another group of cases the fetus will have suffered some asphyxia from excessive interference with uteroplacental circulation, and with the least amount of inhalation anesthesia, it may rapidly develop an asphyxial hemorrhage and die soon after delivery.

There is not sufficient data available at the present time to show how much decrease in fetal and maternal mortality may be accomplished by using, in vaginal deliveries, the strictly conservative treatment as opposed to the version, scalp traction, bagging, or other techniques. Watson[6] reported a small series showing improvement. In our small series of private cases, the conservative treatment has been employed with a fetal mortality much less than the usual percentage given for vaginal deliveries.

In Table I is recorded the material from the St. Joseph's new Maternity Division. It has been divided into two separate time intervals since the earlier period supplied data for a presentation before a local gathering of physicians. The more recent period, then, brings the data up to date. The great differences in incidence of placenta previa in the two time periods are not readily explainable. Only the incidence in the past year corresponds favorably with that reported by Stander[7] for the New York Lying-In Hospital. It is most probably the true incidence for our hospital service since the records recently have been more accurately kept. In this connection, it should be pointed out that the staff of the St. Joseph's Maternity is heterogeneous though fairly well controlled by an organized consultation system.

TABLE I. INCIDENCE OF PLACENTA PREVIA IN TERM AND NEAR TERM DELIVERIES AT ST. JOSEPH'S MATERNITY

Deliveries 1939 to October, 1943	19,588
Number of cases of placenta previa	48
Incidence 1 in 408	
Deliveries October, 1943, to October, 1944	5,038
Number of cases of placenta previa	31
Incidence 1 in 162	
Deliveries 1939 to October, 1944	24,626*
Number of cases of placenta previa	79
Incidence 1 in 347 (Stander, 1 in 180)	

*211 sets of twins.

TABLE II. CORRECTED FETAL MORTALITY IN 79 CASES OF VARIOUSLY TREATED PLACENTA PREVIA (82 FETUSES)

METHOD OF DELIVERY	CASES (NO.)	DEATHS (NO.)	FETUSES (NO.)	TOTAL MORTALITY (%)
Cesarean section	42	9	42	21.4
Strictly conservative	29	2	24	8.3
Other techniques	8	5	6	83.3
Totals	79	16	72	22.2

Returning now to fetal mortality as experienced in our largest maternity hospital, Table II, it is seen that corrected figures are given. Only the following ten fetuses were corrected out; prematurity, i.e., less than seven full calendar months gestation (seven cases), stillbirths (two cases, both of which were macerated, one being a case of missed labor), and congenital anomalies incompatible with life (one case). The relatively high mortality for cesarean section deliveries, which is essentially that of the entire series, is discouraging and probably accounted for through the effect of anesthetic agents upon already traumatized fetuses. By strictly conservative treatment is meant no interference with labor or delivery except possibly rupture of membranes, elective low forceps, or breech extraction after full cervical dilatation. This method of handling labor and delivery, exclusive of transfusions or other supportive therapy equally applicable to all other cases, yielded the lowest fetal mortality rate. The worst rate is found in the group treated by other techniques, i.e., all other methods of vaginal delivery. Some of these latter,

notably the intrauterine bag, may have some merit in selected cases. However, others, particularly version with extraction through an incompletely dilated cervix (two cases) and Dührssen's incisions with operative delivery (one case), are to be severely and forever condemned. It must be conceded that the number of cases here presented, and especially the number in each subdivision of type of delivery, is too small to be of absolute statistical value. Nevertheless, each shows a definite trend which cannot be ignored.

The immediate maternal mortality in all cases of placenta previa should be nil or at least should not exceed 1 per cent. Here the cause of death is due to hemorrhage and is seldom, if ever, due to the blood loss of previa alone, but to some additional factor which increases the blood loss, e.g., untimely cesarean section, injury to the cervix, rupture of uterus, and too hasty separation of the placenta during the third stage. There are two rare complications of placenta previa which might prove immediately fatal, namely, massive ablation, and placenta accreta involving the cervix. The remote maternal mortality which is due to infection, though small, will always be present. Even here anemia from blood loss may be a contributing factor through lowering resistance. The maternal mortality in our relatively small total series was nil from all types of delivery.

All cases of suspected placenta previa should be hospitalized for purposes of accurate diagnosis and for close observation of a developing anemia. Hospital rest may also decrease the bleeding episodes while awaiting good viability of the fetus. If, for economic reasons, this is impractical, the patient should be returned to the hospital for careful blood study after each bleeding spell of any consequence.

When the pregnancy is terminated either with the onset of labor or by prearrangement, it will, for purposes of treatment, fall into one of two groups, namely, those best delivered by cesarean section and those best delivered per vaginam. The first group includes all cases of central placenta previa and probably, in the interest of the baby, practically all previas in primiparas. This arrangement leaves for the second group those cases of partialis and marginalis occurring in multiparas. In the first group it is imperative only that the operator make sure that the operation is done at the safe time, i.e., that the blood pressure be sufficiently high to withstand the sudden additional blood loss following separation of the placenta. Furthermore, the anesthetic should be as light and short as possible and the one which is least conducive to circulatory collapse.

Inasmuch as the incidence of placenta previa increases with multiparity, the second group will include a large number of cases. It is for this group that the writer strongly advocates the ultraconservative treatment as opposed to bagging, version, scalp traction, etc. It is helpful for one using it to have the earnest and positive conviction that untraumatized and unhurried previas do not bleed to death. Otherwise, a puddle of blood may cause one to change the treatment at the wrong time and with dire consequences.

The patient is taken to the delivery room and prepared and draped for delivery. This is not done with the idea that delivery or transfusion may be necessary, but because the delivery room is the cleanest and handiest place to rupture the membranes. With the utmost care the middle finger of the left hand seeks a place near the edge of the placenta where the membranes alone separate the finger from the presenting fetal pole. Using the finger as a director, uterine dressing forceps are passed to contact the membranes.

Then, instead of puncturing them, the tips are used to bite a perforation. The forceps are inserted further and opened in order to produce a large rent. This allows the amniotic fluid to escape freely. The patient is returned to her room. As labor progresses, the presenting pole aids the dilatation and acts as a natural tampon. In addition, the escape of the amniotic fluid decreases the intrauterine volume and permits of at least a certain amount of retraction in the lower uterine segment. This may be a valuable aid in preventing blood loss. The labor is then watched with frequent checking of the blood loss, blood pressure, and fetal heart. Everything should be done to make the labor as comfortable and slow as possible. It should not be necessary to say that a suitable donor whose Rh possibilities have been determined should be available. Plasma may be used to great advantage during the emergency, reserving the blood donor for the treatment of a possible postpartum hemorrhage or anemia.

The patient is returned to the delivery room at the end of the first stage of labor. At the completion of the second stage, which may end spontaneously or be assisted with outlet forceps delivery, the uterus may be gently supported, but no effort should be made to hasten separation of remaining attached placental tissue. This is especially true if free bleeding is present. There is no blood escaping from unabrupted uteroplacental sinuses, and to provide a fresh source of bleeding may be the determining factor in the outcome. Allow the placenta to separate naturally.

It is not presumed that every patient with a nonviable fetus and placenta previa should be carried along indefinitely. The tendency has always been to interfere at too early a stage in pregnancy. Our contention, however, is that it is safe for both mother and child, provided the mother's blood picture is followed carefully. This must be the criterion for interruption of the pregnancy before the fetus has reached easy viability, and not an alarming history derived from a lay estimate of the amount of blood lost. Procrastination must end when the total blood loss has produced a secondary anemia of such severity that further bleeding would endanger the life of the mother.

In conclusion, may I, for statistical purposes, make the following request? will you please report to me any fatal case of placenta previa which you may know about where there had been no cervical nor intrauterine manipulation, nor any attempt at manual removal of remaining placental tissue during the third stage of labor. I promise to reward you and will add your case to my series. This offer has been made many times during the last fifteen years, and at many of the "refresher courses" offered by the State of Texas several years ago. These courses were attended by many of the older practitioners. I have, as yet, no case with which to start the series. Certainly, somewhere, sometime, someone must have died from placenta previa without having received energetic or heroic treatment.

Conclusions

1. It is suggested that obstetric textbooks be revised as regards maternal prognosis in placenta previa.

2. No maternal death from placenta previa has been seen where Nature has been allowed to take its course as regards labor and delivery.

3. All cases of vaginal bleeding in the last trimester should be subjected to careful examination in the hospital with the view to rule out placenta previa.

4. Vaginal examination is essential for accurate diagnosis, but there are several valuable aids whose merits are presented.

5. The mechanics of cervical dilatation and of placental separation in placenta previa are discussed.

6. Reasons for the improbability of a patient spontaneously bleeding to death from placenta previa are given.

7. Hospitalization from the first episode of vaginal bleeding through labor and delivery is urged.

8. The maternal mortality for all types of delivery in the small series reported (79 cases) was nil.

9. The fetal mortality was average in cesarean section deliveries. It was lowest in conservative vaginal deliveries.

References

1. Stander, H. J.: Williams Text-Book of Obstetrics, ed. 8, New York, 1941, D. Appleton-Century Co., p. 1061.
2. Greenhill, J. P.: Principles and Practices of Obstetrics, ed. 8, Philadelphia, 1943, W. B. Saunders Co., p. 459.
3. Beck, Alfred: Obstetrical Practice, ed. 3, Baltimore, 1942, Williams & Wilkins Co., p. 696.
4. Dippel, A. L., and Brown, W. H.: Am. J. Obst. & Gynec. **40**: 986, 1940.
5. Greenhill, J. P.: Am. J. Obst. & Gynec. **37**: 624, 1939.
6. Watson, B. P.: Am. J. Obst. & Gynec. **46**: 524, 1943.
7. Stander, H. J.: Williams Text-Book of Obstetrics, ed. 8, New York, 1941, D. Appleton-Century Co., p. 1058.

RESULTS OF VARIOUS TYPES OF TREATMENT IN ADENOCARCINOMA OF THE ENDOMETRIUM

Chas. E. McLennan, M.D., Ph.D., Salt Lake City, Utah

(From the Departments of Obstetrics and Gynecology, University of Minnesota and University of Utah Schools of Medicine, and the University of Minnesota Hospitals, Minneapolis)

During the years 1928 to 1943, inclusive, 225 women with carcinoma in the body of the uterus were observed in the University of Minnesota Hospitals. Of these, 111 were seen more than five years ago; 114 were handled after Jan. 1, 1939, and are considered separately, since they have not passed through the required five-year observation period. All of these patients have been followed to the present time or until death. In all instances histologic proof of the carcinoma was obtained. Fifty of the 111 were living and free from recurrence five years after treatment, an absolute cure rate of 45 per cent. The relative cure rate, based on 106 patients given some form of therapy, is 47 per cent. Since only 80 of the 111 patients were treated primarily at the University Hospital, while 31 had had some form of treatment elsewhere, the material has been divided into these two groups for detailed consideration. Seventy-six of the 80 women *not previously treated* were given therapy at the University Hospital, and 34 were living and free from recurrence five years after treatment. Thus, the relative cure rate for this group is 44.7 per cent and the absolute cure rate 42.5 per cent.

Material

Table I shows the varieties of treatment given to the 80 patients referred without preliminary therapy. More than half (46) of these were treated by irradiation alone (radium and/or x-ray). Five others were treated initially with radium and x-ray, hyster-

ectomy being done from one and one-half to six years later because of local recurrences. The reasons for not performing hysterectomy in the 46 patients treated by irradiation alone are shown in Table II. It will be seen that 26 patients were considered inoperable on the basis of actual or possible extension of carcinoma beyond the uterine corpus. Only 13 of these had proven metastases (largely vaginal), the other 13 presenting some induration in the broad ligament areas. In view of the comparatively poor end results in the irradiated group, it may have been advisable, in retrospect, to have subjected to laparotomy most of the patients with minor metastases and certainly all who exhibited merely questionable thickening in the broad ligaments. The five-year cure rate for 29 patients subjected to total hysterectomy (Table I, items 1-5) was 83 per cent, whereas only 22 per cent of the 46 irradiated patients lived more than five years. The latter group, of course, contained all of the surgically "bad risk" patients, as well as those with extensive tumors, but it seems likely that a much greater percentage of the patients could have withstood operation successfully. On the basis of our experience in the past five years, it appears that approximately 30 per cent of patients with carcinoma of the fundus are not good candidates for surgical therapy when first seen.

Table III gives the end results for 31 patients treated to some extent before presenting themselves at the University Hospital. While one might anticipate poor results in this group, the five-year cure rate of 57 per cent does not confirm this expectation. The good result in the small group treated by subtotal hysterectomy elsewhere is particularly surprising, but presumably represents the fact that these lesions, fortunately, were early and well localized. The apparently favorable outcome in this group should not by any means be interpreted as an indication for subtotal removal of the uterus in carcinoma of the fundus. Those receiving radium elsewhere were, for the most part, treated similarly to those treated primarily in the University Hospital (i.e., x-ray or hysterectomy following radium) and the results are comparable to those in the primary group. The 12 patients

TABLE I. ADENOCARCINOMA IN CORPUS UTERI, 1928 TO 1938: VARIETIES OF THERAPY IN PATIENTS NOT PREVIOUSLY TREATED ELSEWHERE

TREATMENT	NO.	5-YEAR CURE RATE (%)
1. Radium, x-ray, total hysterectomy	1	100.0
2. Radium, hysterectomy, postoperative x-ray	17	82.3
3. Hysterectomy, postoperative x-ray	3	100.0
4. Radium, hysterectomy (1 postoperative death)	3	66.7
5. Radium, x-ray; hysterectomy for recurrence 1½ to 6 years later	5	80.0
6. Subtotal hysterectomy, postoperative radium and x-ray	1	0.0
7. X-ray followed by radium	4	0.0
8. Radium followed by x-ray	38	26.3
9. X-ray only	4	0.0
10. No treatment	4	0.0

TABLE II. ADENOCARCINOMA IN CORPUS UTERI, 1928 TO 1938. REASONS FOR USING ONLY IRRADIATION IN 46 CASES

REASONS	NO. OF CASES
1. Actual or possible extension of tumor beyond body of uterus	26
2. Old age (over 70 years)	7
3. Diabetes mellitus	5
4. Pelvic inflammation following radium	2
5. Corpus tumor mistaken for primary cervical tumor	2
6. Heart disease	2
7. Carbuncle of abdominal wall	1
8. Obesity (330 pounds) and hypertension	1

TABLE III. ADENOCARCINOMA IN CORPUS UTERI, 1928 TO 1938. RESULTS IN PATIENTS TREATED TO SOME EXTENT ELSEWHERE

TREATMENT ELSEWHERE	NO.	LIVING 5 YR. AFTER TREATMENT HERE	5-YEAR CURE RATE PER CENT
Total hysterectomy	12	5	41.7
Subtotal hysterectomy	9	7	77.8
Radium in uterine cavity	10	5	50.0
Total	31	17	56.7*

*Relative rate, based on 30 patients given further treatment.

who had had total hysterectomy done elsewhere were admitted largely because of vaginal metastases. *Irradiation salvaged 42 per cent of these for at least five years.*

During the years 1939 to 1943, inclusive, 114 new patients with carcinoma of the uterine body were observed. Twenty-one of these women had been subjected to some form of therapy elsewhere. Table IV shows the nature of the treatment given to the 93 patients who had not been treated previously. Tables V and VI reveal the reasons for incomplete therapy in 27 instances and nonroutine management in 17 other patients. From the beginning of 1939 until July 1, 1941, standard or "routine" therapy for carcinoma in the uterine corpus consisted of deep x-ray, intrauterine radium, and total hysterectomy, in that order. The dosage of x-ray amounted to 250 to 300 per cent skin-erythema dose delivered to the site of the tumor in 25 to 30 daily treatments over approximately four weeks. Radium then was applied from five intrauterine portals, and a dose of 5,000 mg. hours was given over a period of 100 hours. Four to six weeks after the completion of the irradiation therapy, total hysterectomy and bilateral salpingo-oophorectomy were carried out by the abdominal route.

It should be noted that only 53 per cent of the patients received "routine" treatment. In other words, in nearly half of the patients there were reasons for breaking through a carefully planned therapeutic sequence. While it is true that approximately 70 per cent of the patients were subjected to "complete" or adequate therapy, in the sense that total removal of the uterus was effected, it is obvious that the treatment in some of these women cannot be viewed as satisfactory from the standpoint of having eradicated all the demonstrable malignant tissue. Thus, something between 50 and 70 per cent of the previously untreated patients may be said to have a chance of five-year survival on the basis of treatment instituted when first seen. That is, at least 50 per cent but not over 70 per cent of the patients received a form of therapy designed to be completely curative. In material of this sort it seems unreasonable to anticipate anything better than a five-year cure rate of *about* 60 per cent, and even this would entail an almost perfect end result in those without obvious metastases at the time of treatment.

Table VII shows the present status of the 114 women seen in the last five years. Only one patient receiving "routine" treatment has died from recurrent carcinoma. This 65-year-old woman was treated in June, 1942, with our present routine of radium followed by hysterectomy, and died in September, 1943, with a massive recurrence of pelvic carcinoma. One routinely treated patient died postoperatively of bronchopneumonia after the abdominal wound had separated completely on two occasions. She had been treated with a full course of x-ray as well as radium preoperatively. A third patient in the routinely treated group died of heart disease two and one-half years after treatment of the carcinoma. Autopsy showed no evidence of recurrent tumor. Only one-fourth of the patients receiving incomplete therapy have survived from 0 to 4 years and the ultimate five-year survival in this group may be ex-

TABLE IV. ADENOCARCINOMA IN CORPUS UTERI, 1939 TO 1943. THERAPY GIVEN 93 PREVIOUSLY UNTREATED PATIENTS

TREATMENT		NO.	PER CENT OF TOTAL
1. "Complete" treatment: hysterectomy with or without irradiation		66	70.9
X-ray, radium, hysterectomy	22		
Radium and hysterectomy	27		
Hysterectomy alone	11		
X-ray and hysterectomy	3		
Hysterectomy, postoperative radium	1		
Hysterectomy, postoperative x-ray	1		
Radium (partial dose), hysterectomy, postoperative x-ray	1		
2. "Routine" treatment: radium ± x-ray, total hysterectomy in 4 to 6 weeks		49	52.6
3. Other varieties of treatment		27	29.1
Intrauterine radium only	12		
x-ray and radium	6		
X-ray only	2		
Exploratory laparotomy	1		
Subtotal hysterectomy, postoperative x-ray and radium	1		
Subtotal hysterectomy (extensive metastases at operation)	1		
No treatment	4		

TABLE V. ADENOCARCINOMA IN CORPUS UTERI, 1939 TO 1943. REASONS FOR INCOMPLETE THERAPY IN 27 PATIENTS

REASONS	NO. OF CASES
1. Obvious metastases when first examined	9
2. Heart disease	6
3. Obesity and hypertension	3
4. Primary malignant disease elsewhere	2
5. Irradiation death prior to hysterectomy	2
6. Advanced age (75 years or above)	2
7. Uremia following irradiation (death)	1
8. Operation refused	1
9. Multiple sclerosis	1

TABLE VI. ADENOCARCINOMA IN CORPUS UTERI, 1939 TO 1943. REASONS FOR NONROUTINE THERAPY IN 17 PATIENTS

REASONS	NO. OF CASES
Uterus perforated during attempt at radium insertion	1
Curettage negative (false cavity made in wall); hysterectomy without preliminary radiation	1
Myomata uteri	2
Vaginal metastases present, others suspected	2
Pelvic inflammatory disease	2
Diabetes and obesity	1
Psychosis	1
Diarrhea during irradiation	1
Leucopenia during irradiation	1
Febrile reaction from radium	1
Ovarian cystoma	1
Question of primary gastric tumor (immediate laparotomy)	1
Extrauterine mass of unknown origin (metastatic tumor in iliac lymph nodes)	1
Operator's decision to omit radiation (private patient)	1

TABLE VII. ADENOCARCINOMA IN CORPUS UTERI, 1939 TO 1943. PRESENT STATUS OF 114 PATIENTS OBSERVED LESS THAN FIVE YEARS

THERAPEUTIC GROUP	NUMBER LIVING 0-4 YEARS	PER CENT OF GROUP
66 given "complete" treatment (3 deaths from intercurrent disease)	56	84.8
49 given "routine" treatment (Deaths: 1 intercurrent disease, 1 postoperative, 1 recurrent carcinoma)	46	93.8
27 given incomplete or no therapy	7	25.9
93 given no treatment elsewhere	63	67.7
21 treated elsewhere previously	14	66.7

TABLE VIII. RESULTS OF TREATMENT IN ALL CASES OF ADENOCARCINOMA IN CORPUS UTERI, 1928 TO 1943

YEAR	NUMBER OF CASES	LIVING AND WELL AFTER A PERIOD OF OBSERVATION OF YEARS														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1928	3	1	1	1	1	1 (33.3%)	1	1	1	0	0	0	0	0	0	0
1929	6	5	4	4	4	4 (66.7%)	4	4	4	4	4	3	3	3	3	–
1930	3	3	3	2	2	2 (66.7%)	2	2	2	2	2	2	2	2	–	
1931	11	4	3	2	2	2 (18.2%)	2	2	2	2	2	2	2	–		
1932	7	5	4	4	4	4 (57.2%)	3	2	2	2	2	2	–			
1933	12	8	6	6	5	5 (41.7%)	5	5	5	5	5	–				
1934	12	6	5	5	4	4 (33.3%)	4	4	4	3	–					
1935	13	10	9	8	6	6 (46.2%)	6	5	5	–						
1936	12	8	8	8	7	6 (50.0%)	6	6	–							
1937	17	13	11	8	8	8 (47.1%)	8	–								
1938	15	8	8	8	8	8 (53.3%)	–									
Total	111	71	62	56	51	50 (45.0%)										
1939	25	16	15	13	12	– –										
1940	23	16	13	13	–											
1941	19	14	14	–												
1942	25	18	–													
1943	22	–														
Total	225															

pected to be exceedingly low. It is interesting to note that there is to date no difference between the survival rate of patients treated to some extent elsewhere and those treated primarily in the University Hospital. This has already been demonstrated for the patients treated prior to 1939, and is quite the opposite of our results in women with carcinoma of the uterine cervix. The results of treatment in *all* cases of carcinoma of the uterine body, in terms of absolute survival and cure rates, are depicted in Table VIII.

Table IX shows the operative mortality for all patients with adenocarcinoma of the uterine body who have been subjected to major surgical procedures. The gross surgical mortality over sixteen years has been 5.8 per cent, but when three patients with virtually hopeless prognosis prior to operation are excluded, the over-all rate becomes 3 per cent. Details concerning the six postoperative deaths are given below. It should be noted that only 24 per cent of 111 women were treated surgically from 1928 to 1938, while approximately 68 per cent of the last 114 patients were subjected to operation. The corrected primary operative mortality rate for the last five years is 1 per cent below that for the period 1928 to 1938, but the significance of this is open to serious question because of the comparatively small number of cases in the earlier group.

TABLE IX. OPERATIVE MORTALITY IN ADENOCARCINOMA IN CORPUS UTERI, 1928 TO 1943

PERIOD	NUMBER OF PATIENTS OPERATED	NUMBER OF POSTOPERATIVE DEATHS	MORTALITY RATE PER CENT
1928-1943	104	6	5.8
1928-1938	27	1	3.7
1939-1943	77	5	6.5
1939-1943, corrected*	74	3	2.7
1928-1943, corrected	101	2	3.0

*See explanation in text.

Postoperative Deaths

1. H. G., No. 626016, age 63 years, admitted July 16, 1934, died July 22, 1934. Had hypertensive heart disease, blood pressure 180/105. Preliminary treatment with 2,400 mg. hours of radium in March, 1934. Failed to return for hysterectomy until four months later. Became irrational on first postoperative day, temperature rose to 105° F., and death ensued on third day. Autopsy did not confirm clinical diagnoses of peritonitis and bronchopneumonia. The heart showed coronary sclerosis and there was questionable evidence of occlusion of the anterior descending branch of the left coronary artery.

2. E. C., No. 679832, age 41 years, weight 190 pounds, admitted April 19, 1939, for course of deep x-ray and radium, discharged June 6, 1939, readmitted June 27 for hysterectomy, died Aug. 3, 1939. Total hysterectomy and bilateral salpingo-oophorectomy were carried out on June 30. Complete separation of the abdominal wound occurred on the twelfth postoperative day and secondary closure was done by layers. Dehiscence recurred eight days later, at which time there was evidence of bronchopneumonia. The course was progressively worse despite oxygen, sulfonamides, and blood transfusions. Autopsy was not permitted, but inspection of the abdominal cavity through the operative site showed no gross evidence of peritonitis.

3. R. C., No. 626417, age 68 years, weight 203 pounds, had received radium and x-ray therapy in 1935 for adenocarcinoma of the uterine corpus. This therapy was repeated in 1937 when recurrent tumor appeared. She was admitted Aug. 9, 1939, for surgical treatment of a second recurrence. Following total abdominal hysterectomy on August 25 she developed a pelvic abscess and died on the tenth postoperative day. Autopsy revealed, in addition to the pelvic infection, questionable evidence of pulmonary embolism.

4. A. P., No. 688249, age 37 years, weight 288 pounds, admitted Nov. 14, 1939, with vaginal and vulvar metastases from adenocarcinoma of the uterine corpus. Exploratory laparotomy on November 28 showed extension of tumor to the aortic lymph nodes, and only a right salpingo-oophorectomy was done. She expired on the third postoperative day after a temperature rise to 108° F. Autopsy failed to reveal any explanation for the sudden death other than the clinical picture of hepatorenal syndrome.

5. M. T., No. 717690, age 67 years, weight 159 pounds, admitted Feb. 10, 1942. Hysterectomy was done on February 19 without preliminary irradiation because of the pres-

ence of an adnexal mass, which was found to be a myoma. Death on the eighth postoperative day was attributed to septicemia, although bacteriologic proof of this could not be established. Autopsy was limited to the abdominal cavity and was not helpful in establishing the cause of death.

6. I. P., No. 725559, age 55 years, admitted Oct. 18, 1942, with pelvic carcinomatosis and vaginal metastases. Laparotomy was done on October 23 to remove as much tumor as possible prior to palliative x-ray therapy. Uterine fundectomy and bilateral salpingo-oophorectomy were performed. On the thirteenth postoperative day she developed right hemiplegia, went into coma, and died five days later. Autopsy showed metastatic carcinoma in the brain and terminal acute bacterial endocarditis with splenic and renal infarcts.

Group Receiving X-ray Therapy, 1939 to 1941

From Jan. 1, 1939, to July 1, 1941, 38 patients, ranging in age from 40 to 74 years (average of 59), received full or partial courses of deep x-ray. Thirty-one were previously untreated. In three of these the x-ray was given as a palliative procedure, and complete therapy, including hysterectomy, was not contemplated. There remain, then, 28 patients to whom deep x-ray was administered as the first step in a plan of "complete" or "routine" therapy. (See above for definition.)

The entire planned therapy was completed by only 18 (64 per cent) of these patients. X-ray was discontinued in three because of nausea, vomiting, and diarrhea, and in one because of a severe leucopenia. In two, only a partial dosage of radium was given and one of these was not subjected to hysterectomy because of pelvic infection and general debility associated with advanced age. One received no radium because the uterus was accidentally perforated during an attempt at application, and in another the radium was omitted because of the severity of the gastrointestinal disturbance during a partial course of x-ray. Three patients died following irradiation before they could be subjected to hysterectomy, and no hysterectomy was done in the elderly woman mentioned above. Of the three dying soon after irradiation, one developed uremia, one had peritonitis following perforation of a radiation ulcer in the colon, and the third was a diabetic who developed a severe febrile reaction a week after completing her irradiation. She died within a few days despite adequate control of the diabetes, and permission for autopsy could not be obtained. The only obvious cause of the high fever was a pyogenic skin infection.

In the group of seven patients who had previously been treated to some extent, x-ray therapy had to be discontinued in two instances, once because of nausea and vomiting, and once because of severe diarrhea.

Secondary anemia, as indicated by a hemoglobin level of less than 10 grams per 100 c.c. of blood, developed in two patients during irradiation therapy. Leucopenia (less than 3,000 white blood cells per cu. mm.) developed in seven patients. In one of these the x-ray treatments were stopped entirely, in the others only intermittently. Twenty-one of the 38 irradiated patients had diarrhea during the therapy, 12 complained of nausea and vomiting, 3 developed evidence of acute pelvic inflammatory disease, 2 complained of persistent abdominal pain, and in one an old colostomy site, which had been closed surgically, reopened spontaneously.

Seven out of 20 uteri which were completely irradiated subsequently showed histologic evidence of viable carcinoma at the time of hysterectomy or autopsy. In 6 patients who were incompletely irradiated, 5 of the uteri contained carcinoma following hysterectomy. Further details concerning the histologic findings in our irradiated corpus tumors are reported elsewhere (Stowe). It is also interesting to note that myomata uteri were found in 7 out of the 28 patients in this series who were subjected to either hysterectomy or autopsy.

TABLE X. ADENOCARCINOMA IN CORPUS UTERI, JANUARY, 1939, TO JULY, 1941. SURVIVAL OF PATIENTS RECEIVING DEEP X-RAY THERAPY

	LIVING AND WELL 3 TO 4½ YR.	LIVING WITH RECURRENCE	DEAD
Entire group of 38 patients	23 (61%)	2	13
31 not previously treated	19 (61%)	2	10
7 previously treated elsewhere	4 (57%)	0	3
18 who completed full therapy	15 (83%)	1	2*
10 who had less than full therapy	4 (40%)	0	6

*One death from intercurrent disease (cardiac), one postoperative.

Table X gives the results of treatment of the 38 irradiated women in terms of survival from 3 to 4½ years after therapy. It may be seen that approximately 60 per cent have survived, and that there is no appreciable difference between the group not previously treated and the group which had been given some form of therapy elsewhere. The survival rate for the 18 who went through the complete therapeutic plan is 83 per cent. This figure would have been 100 per cent had there not been one postoperative death (wound disruption and pneumonia) and one death from heart disease (see above). Only 4 of the 10 women who were unable to complete full therapy are alive at present.

Discussion

Hysterectomy generally is conceded to be the important part of the therapy for carcinoma of the uterine body. In recent years the only objection to this concept has been raised by Heyman at the Radiumhemmet in Stockholm where specialized techniques for the application of intracavitary radium are employed in the primary therapy. The question to which an answer is being sought currently in many gynecologic clinics is whether the preoperative addition of radium and/or x-ray therapy will materially increase the survival rates in operable cases. Some investigators seem to feel that this question has long since been settled in favor of preliminary irradiation, but it should be noted that the surgical results used for comparisons often antedate the irradiated material by many years. The two sets of data, then, are not exactly suitable for comparison since many extraneous factors may have influenced the final results. It seems unlikely that this question will be settled until alternation of hysterectomy with and without preceding irradiation has been carried out in sufficient numbers of patients to warrant statistical analysis of the results.

The experience reviewed here leads to a number of apparent conclusions, some of which have already been mentioned in describing the results. The poor results obtained in the group treated with a single radium applicator in the uterine cavity, with or without the addition of deep x-ray, strongly suggest that this is an incomplete form of treatment. Whenever possible, total hysterectomy should follow irradiation. Operability cannot be determined routinely on the basis of bimanual pelvic palpation.

While the virtues of standardized treatment for various types of malignant tumors are now generally recognized, this study demonstrates the difficulties which arise when an attempt is made to subject a large number of elderly women to a standard therapeutic plan. It was found, for example, that only 53 per cent of the patients received "routine" treatment, and that only 71 per cent were adequately treated in the sense that hysterectomy was performed. The salvage in the group which could not be hysterectomized will, after five years, be extremely small. Many of these were beyond real help when first seen. While it appears that 100 per cent of those receiving routine therapy might ideally be expected to survive, accidental deaths within this group will inevitably reduce the final figure by 10 or 20 percentage points. The final survival or cure rates, then, can be estimated fairly well in advance from the nature of the treatment which it has been possible to provide. This is shown particularly well in the small group given deep x-ray therapy from 1939 to 1941. Approximately 60 per cent went through the full therapeutic program, and approximately 60 per cent have survived for three to four and one-half years. The five-year figure may be expected to be somewhat below the percentage of patients subjected to full therapy.

The immediate undesirable effects of giving full-tolerance doses of x-ray to patients with carcinoma of the uterine corpus suggest that persistence with

this part of the therapy will add little or nothing to the ultimate cure rates. Certainly in this small series the primary mortality attributable to irradiation was excessive (8 per cent), and the morbidity likewise was great. One gets the impression that the acute complications of irradiation therapy are comparatively enormous in elderly women of poor general physical status, many of whom are obese, and it should be emphasized that the patients in question here were hospitalized throughout the course of x-ray treatments and were given extraordinary attention with a view to minimizing complications. When it became obvious that the morbidity and mortality were abnormally high in this group of patients, we no longer felt justified in continuing preoperative deep x-ray as a part of the routine treatment. It should be noted, however, that this has not been the experience in certain other clinics, but it is difficult to determine from the literature whether comparable amounts of x-ray therapy were administered over similar periods of time.

It is, of course, too early to evaluate the results of treatment with radium and hysterectomy in patients seen since July, 1941, but it may be said that the trend in survival rates is reasonably favorable up to the present time. There continues to be approximately a 30 per cent loss in the first full year after the year of treatment, inasmuch as this share of the total group represents patients whose prognosis is virtually hopeless from the beginning.

Nothing is to be gained, particularly, by comparing the results of treatment in the series reported here with results previously recorded in the literature. For reports of five-year cure rates ranging from 38 to 74 per cent the reader is referred to the papers of Healy and Brown, Miller, Masson and Gregg, Ward, Watkins and Neilson, and Scheffey et al. The recent report of Schmitz and his co-workers describes the effects of high voltage x-radiation (800 kv.) on the uterus containing adenocarcinoma, but the patients so treated had been followed for only short periods of time.

Summary and Conclusions

The results of treatment in the University of Minnesota Hospital of 225 patients with adenocarcinoma of the uterine corpus have been reviewed. One hundred and eleven of these were seen more than five years ago. No patient has been lost in the follow-up program.

The absolute five-year cure rate has been 45 per cent, including certain patients previously treated elsewhere. The exclusion of these latter patients does not improve the end results.

Poor results are shown to follow routine use of radium and x-ray alone. Certain patients so treated may be salvaged even many years later by hysterectomy for recurrent or perhaps persistent carcinoma.

Good results have followed the use of total hysterectomy, with or without preoperative or postoperative irradiation.

Since the beginning of 1939, only 53 per cent of the patients have been able to go through a planned, standardized routine of treatment. The reasons which necessitated modifying the standard therapy are shown in detail. Approximately 70 per cent of the patients were given what might be termed adequate treatment, in the sense that total hysterectomy was performed.

In the past five years only one patient out of the group receiving routine or standardized treatment has died of recurrent carcinoma.

The operative mortality for the entire series has been 5.8 per cent uncorrected, or 3 per cent, corrected (see text).

The results in terms of immediate morbidity and mortality in 38 patients given full-tolerance doses of deep x-ray preceding intrauterine radium and hysterectomy were undesirable. It is suggested that preoperative deep x-ray therapy will add nothing to the ultimate cure rates.

No conclusions can as yet be drawn from recent experience with intrauterine radium followed in four to six weeks by total hysterectomy.

The final results in the treatment of carcinoma of the uterine corpus are predetermined to a considerable extent by the nature of the material presented for therapy, in terms of metastases, medical and surgical complications, age, weight, and nutritional status.

References

Healy, W. P., and Brown R. L.: Am. J. Obst. & Gynec. **38**: 1, 1939.
Heyman, J., Reuterwall, O., and Benner, S.: Acta radiol. **22**: 11, 1941.
Masson, J. C., and Gregg, R. O.: Surg., Gynec. & Obst. **70**: 1083, 1940.
Miller, N. G.: Am. J. Obst. & Gynec. **40**: 791, 1940.
Scheffey, L. C., Thudium, W. J., and Farrell, D. M.: Am. J. Obst. & Gynec. **46**: 786, 1943.
Schmitz, H. E., Sheehan, J. F., and Towne, Janet: Am. J. Obst. & Gynec. **45**: 377, 1943.
Stowe, L. M.: To be published in Am. J. Obst. & Gynec.
Ward, G. G.: Am. J. Obst. & Gynec. **44**: 303, 1942.
Watkins, R. E., and Neilson, D. R.: West. J. Surg. **50**: 17, 1942.

STUDIES IN AMENORRHEA, OLIGOMENORRHEA, AND ANOVULOMENORRHEA

I. Effect of Equine Gonadotrophin Upon Establishment of Cyclic Menses and Ovulation

A. R. Abarbanel, A.B., M.D., and J. H. Leathem, A.B., M.A., Ph.D.,
Washington, D. C.

(From the Department of Obstetrics and Gynecology, George Washington University School of Medicine, Washington, D. C., and the Department of Zoology, Rutgers University, New Brunswick, N. J.)

Introduction

Among the many desiderata of gynecic endocrine therapy, has been the evolution of a gonadotrophin which would efficiently stimulate the clinically hypofunctioning ovary. Ever since the anterior pituitary-gonadal interrelationship was demonstrated conclusively by Zondek and by Smith and Engle, the clinician has been eagerly awaiting the isolation of a truly potent gonadotrophin. Scores of substances have been brought forth to flourish briefly in the flow of clinical enthusiasm only to fade slowly beyond the horizon on the ebb of critical clinical evaluation and then finally be discarded with the stamp "tried but found wanting."

Recently, a gonadotrophin isolated from the serum of the pregnant mare, known as equine gonadotrophin (hereafter designated as E.G.), has been offered to the medical profession. This gonadotrophin has been found to resemble in its activity certain extracts of the anterior hypophysis, particularly in its ability to produce ovulation in the laboratory animal.[1] The clinical usage of E.G. received an enormous impetus in 1938 when Davis and Koff

reported that they *seemingly* had been able to produce ovulation in the human female with this substance.[2]

Material and Methods

Twenty-two patients were studied. Three had primary amenorrhea, and the remainder secondary amenorrhea, oligomenorrhea, and/or anovulomenorrhea. Each patient was evaluated over a period of three to nine months before any E.G. was administered. Pretreatment data included endometrial biopsies, determinations of the basal metabolic rate, red cell count and hemoglobin, as well as routine urinalysis and, where indicated, x-ray studies of the chest and sella turcica as well as forearm and wrist for bone age. In addition, an attempt was made to have each patient interviewed carefully by a skilled dietitian as to her dietary regime and as to how it was prepared.

If regular menses did not appear after an observation period of three to nine months, adjuvant therapy with equine gonadotrophin was instituted. In some cases, hormone therapy was administered in an effort to produce ovulation in patients who were seemingly not ovulating. The criterion of an ovulatory response was the finding of a secretory endometrium within two to three weeks after therapy. Almost every biopsy was fixed in picric alcohol and stained for glycogen in addition to the routine hematoxylin and eosin stain.

Each course of equine gonadotrophin was usually given over a period of seven to ten days. If 2,000 I.U. were to be administered, the following schedule was ordered: the initial dose of 200 I.U. was followed in two to three days by 400 I.U., then after the same interval by 600 I.U., all intramuscularly. The final dose of 800 I.U. was given intravenously, two to three days later. Occasionally the entire course was given solely by the one or the other route. As a rule, seven to twenty-one days after the last injection of E.G., an endometrial biopsy was secured. In some instances this was purposely omitted.*

Two preparations of E.G. were used. The less purified product was the commercially available one containing 0.0002 mg. of nitrogen per international unit. The other was 2.5 times more highly purified (as regards nitrogen content), containing only 0.00008 mg. per international unit.

Results.—The pertinent data have been presented in Table I, while the results have been summarized in Table II.

Primary Amenorrhea.—Briefly, it was noted that in these three cases, E.G. was without any effect as far as the appearance of menstruation was concerned.

Secondary Amenorrhea.—There were eleven cases of secondary amenorrhea whose duration ranged from four to twenty-six months. In eight of these, equine gonadotrophin proved ineffectual in stimulating either ovulation or the re-establishment of regular menstrual cycles. The remaining two (Cases 10 and 12) apparently did seem to show a transient favorable response to E.G.

In Case 12, endometrial biopsies taken over a period of six months disclosed an early secretory picture on one occasion after an amenorrhea of 5.5 months. Two subsequent biopsies showed a late proliferative phase premenstrually. She failed to menstruate for two months. Accordingly, she was given 4,000 I.U. equine gonadotrophin. Twenty-six days later she began to experience what seemed to be menstrual cramps. She was given 400 I.U. that day, and a week later an endometrial biopsy disclosed a premenstrual secretory phase. However, no menses occurred the following month. At this time, she went to live and work on a farm. Soon thereafter, menses reappeared and then recurred at regular intervals. This good result was most plausibly caused by the adoption of an adequate diet.

The other patient with secondary amenorrhea (Case 10) seemingly ovulated following equine gonadotrophin. This result, however, is open to serious question, because ovulation apparently did not occur in response to E.G. *before* she received thyroid extract, but only *after* she had been on it for three months. Since thyroid extract alone could accomplish the same effect, and did in several other cases, the ovulatory effect cannot indubitably be attributed to the equine gonadotrophin.

Oligomenorrhea.—Of the seven cases in this category, six showed no response to E.G. as far as either ovulation or more regular menses was concerned. In one (Case 9) menses did seem to become more regular following one or more courses of equine gonadotrophin. But it must be emphasized that she was on iron and a special diet at the same time. On

*It was often noted that endometrial biopsy was frequently followed by menstruation. As a result, this procedure was purposely omitted in some cases in order to note whether menses would occur spontaneously.

TABLE 1

CASE NO.	AGE	MENST. & OBST. HISTORY	PRESENT ILLNESS	B.M.R.	R.B.C.	HGB. (%)
1	17	none	primary amen.	+ 4	5.94	80
2	19	none	primary amen.	– 4	4.07	65
3	16	none	primary amen.	–16	4.46	70
4	39	14 × 30 × 4 grav. 0	amen. 7 mo.	+ 3	4.84	85
5	28	15 × 30 × 5 grav. 0	amen. 7 mo.	+13	3.80	65
6	26	12 × 28 × 3 grav. i para i	amen. 2 yr.	–12	3.98	70
7	24	13 × 30 × 4 grav. 0	amen. 5 mo.	+ 7	4.20	80
8	27	16 × 30 × 4 grav. 0	amen. 4 mo. wt. gain 92 lb. in 2 yr. now 242 lb.	+13	3.80	65
9	36	12 × 28 × 7 grav.i para 0	amen. 26 mo.	–10	4.36	78
10	24	12 × 28 × 4 grav. iv para iv	amen. 14 mo.	–13	4.20	80
11	19	13 × 28 × 4 grav. 0	amen. 9 mo.	– 6	4.38	86
12	35	12 × 28 × 4 grav. 0	amen. 5 mo.	– 4	3.40	70
13	18	12 × 28 × 4 grav. i para i	amen. 2 yr.	– 1	5.56	65
14	26	12 × 28 × 3 grav. i para i	amen. 2 yr.	–12	3.98	70
15	36	13 × 30 × 4 grav. 0	menses q. 4-6 mo. for 4 yr.	– 8	3.35	67
16	27	13 × 30 × 5 grav. 0	menses q. 2-4 mo. for 2 yr.	–15	3.38	67
17	24	14 × 30 × 4 grav. 0	menses q. 2-4 mo. for 3 yr. wt. gain 70 lb. now 220 lb.	– 9	4.06	78
18	23	14 × 30 × 3 grav. i para i	menses q. 2-8 mo. for 5 yr.	– 4	4.24	60
19	34	14 × 30 × 2 grav. 0	menses q. 2-4 mo. for 3 yr. wt. 232 lb.	– 1	3.56	65
20	23	12 × 30 × 4 grav. 0	menses q. 2-6 mo. for 2 yr.	+ 4	4.86	82
21	27	13 × 30 = 90x 7-10 grav. 0	1 preg., profuse menses	–19	4.40	76
22	23	13 × 28 × 5 grav. 0	sterile 3 yr.	– 5	4.80	82

*E.P. — Early proliferative.
L.P. — Late proliferative.
E.S. — Early secretary.
S. — Secretory, premenstrual.
E.H. — Endometrial hyperplasia.

ENDOMET. BIOPSY*	PRETREATMENT OBSERVATION (MONTHS)	EQUINE GONADOTROPHIN (I.U.)	ENDOMET. BIOPSY*	FOLLOW-UP AND COMMENT
none	3	4,000		Still no menses 3 mo. later
		4,000		
none	3	4,000		Still amen. 4 mo. later
		4,000		
none	3	4,000		Still amen. 6 mo. later
		4,000		
E.P.	3	4,000		Still no menses 7 mo. later when
		1,000	E.P.	occas. flushes noted
L.P.	3	2,000		No menses in next 3 mo.
E.P.	3	4,000	E.P.	Still amen. 4 mo. later
E.P.		4,000	E.P.	
		2,000	E.P.	
L.P.	8	4,000	E.H.	Still amen. 5 mo. later
L.P.				
S.				
L.P.				
E.P.	6	2,000	L.P.	Still amen. 2 mo. later
E.P.	9	4,000	E.P.	Still amen. 4 mo. later
		4,000	E.P.	
	2	800	L.P.	Secretory phase only after patient on thyroid for 3 mo.
		400		
		800	S.	
E.H.	4	1,200	E.H.	No menses for 2 mo. Later, regular menses with thyroid
L.P.				
E.S.	7	4,000		Remained amen. until diet regulated
L.P.		400	S.	
L.P.				
	5	4,000		Still amen. 3 mo. later; lactation "atrophy" of uterus?
		4,000		
E.P.	3	4,000	E.P.	Still amen. 4 mo. later
E.P.		4,000	E.P.	
		4,000	E.P.	
E.P.	5	2,000	L.P.	Still amen. 6 mo. later
E.P.		4,000	L.P.	
E.P.		2,000	L.P.	
E.P.		1,000	E.P.	
E.P.	6	4,000		Still amen. 9 mo. later
E.P.		4,000	E.P.	
E.P.				
E.P.				
L.P.	7	2,000	L.P.	No menses in 2 mo. Later regulated on thyroid
L.P.				
S.				
E.P.	4	4,000		No menses for 2 mo.
L.P.		4,000		
E.P.	5	4,000		Menses became more regular (on diet and iron also)
L.P.				
L.P.				
L.P.				
L.P.	6	2,000		Menses still irreg. 3 mo. later
L.P.		1,200	L.P.	
E.P.				
L.P.	6	2,000	L.P.	Menses still irreg. Profuse 6
L.P.		4,000	L.P.	mo. later
		4,000	L.P.	
		6,800	L.P.	
L.P.	6	5,000	L.P.	After thyroid for 7 mo. began to ovulate
L.P.				

TABLE II. SUMMARY OF EFFECTS OF EQUINE GONADOTROPHIN

CONDITION	NO. OF CASES	STIMULATION OF	
		OVULATION	CYCLIC MENSES
Primary amenorrhea	3	0	0
Secondary amenorrhea	11	2	1
Oligomenorrhea	7	0	1
Regular anovulomenorrhea	1	0	0
Total	22	2	2

the other hand, biopsies after the administration of this gonadotrophin failed to reveal any evidence as regards stimulation of ovulation.

Cyclic Anovulomenorrhea.—The patient with regular anovulomenorrhea (Case 22) did not respond to equine gonadotrophin but eventually did to thyroid extract.

Comment.—It might be mentioned in passing that 9 of these 22 cases were eventually salvaged by means of an adequate, properly balanced, and properly prepared diet alone, or in conjunction with thyroid extract.

Discussion

Review of the clinical literature indicates that the efficiency of equine gonadotrophin in the management of the abnormally or hypofunctioning ovary in the human being has often been viewed in a favorable light. Some observers have been reserved in their conclusions. In contrast, others have reported entirely negative results. (For review of literature, see Davis[3] and Erving et al.[4])

Erving, Sears, and Rock, in a carefully presented and detailed report of treatment of 48 cases of amenorrhea, dysfunctional bleeding, and sterility with equine gonadotrophin, concluded that "equine gonadotrophic hormone has not been shown to stimulate ovulation in women with anovulatory bleeding or amenorrhea nor has it any apparent effect in cases of sterility."[4] Brewer, Jones, and Skiles[5] obtained two questionable ovulatory responses to equine gonadotrophin in 24 patients. Vogt and Sexton[6] obtained no evidence of ovulation in 13 cases. Emge[7] observed no response in ten cases of secondary amenorrhea. In this respect, it should be noted that the three failures reported by Davis and Koff[2] were all cases with endometrial hyperplasia. These results are in accord with our findings.

The experimental data of Hartman deserves careful attention. This skillful, experienced, and sagacious observer was able to keep his female monkeys under lock and key and thus carefully supervise them for a long control period. These monkeys exhibit a very high incidence of anovulatory menstrual cycles during the nonbreeding season. Using E.G., Hartman[8] obtained only 7 instances of apparently successfully ovulations in 104 attempts. In 16 cases, abnormal stimulation was evidenced by overdistention of the follicles, hyperplasia of the granulosa cells, as well as an increased number of large cystic follicles. In line with the latter, some investigators have noted suggestive evidence of increased estrogenic output, presumably from ovarian stimulation, the criterion of which was increased proliferation of the endometrium.[6] In the human ovary, Greenblatt[9] and Geist, Gaines, and Salmon[10] noted that some cases exhibited proliferation of the granulosa cells and slight proliferation and occasional luteinization of the theca interna cells, but no instance of ovulation was found which could be indubitably attributed to equine gonadotrophin. In this series, one case showed abnormal stimulation as witnessed by the appearance of cystic glandular hyperplasia after therapy, while a second developed further proliferation of the endometrium. No evidence of ovarian cyst was observed, although such an occurrence has been reported.[4]

As far as stimulation of ovulation is concerned, the gonadotrophic influence of equine gonadotrophin upon the hypofunctioning human ovary still remains to be proved. Moreover, our data indicate that the development of antagonistic substances to E.G. (antigonadotrophins?) does not explain the negative results obtained, because in the groups treated with the more highly purified preparations of E.G., antagonists to E.G. were rarely evoked.[11]

Comment

Adoption of the viewpoint that these functional disorders of menstruation are in reality local manifestations of a constitutional disturbance seems most nearly to approach the basic facts. Fundamentally, such ovarian dysfunction most frequently reflects disturbances in the metabolism of the individual in general. As a result, there occurs a disruption in the normal metabolic cycle of the endocrine glands themselves, the recipient end organs, or both. Two of the important basic factors essential for the normal metabolic functioning of the intricate human machine are the nutritional intake and its utilization, and the thyroid hormone.

Diet is of fundamental importance because each of us actually represents the sum total of what he eats and drinks and how the body utilizes these substances. For a long time, clinical as well as experimental evidence has been at hand to show that the functional, and eventually the structural, integrity of the reproductive systems is largely dependent upon an adequate and nutritionally balanced diet.[12] Obviously, then, when nutritional insults have been heaped for years upon the body in general, and the reproductive organs in particular, regressive structural changes may take place that in time become irreversible. If such is true, then an explanation is at hand for the failure of several of these cases to respond to diet and thyroid.

The general metabolic stimulus of the thyroid hormone has long been recognized. What has been less generally realized by the clinician is the relationship between the thyroid and the pituitary on one hand and the pituitary-gonadal relationship on the other. From the experimental evidence at hand, thyroid deficiency results in regressive changes in cells of the anterior pituitary. Since the latter in turn secretes the gonadotrophic substances essential for normal functioning of the gonad (production of gametes and internal secretions), regressive changes result in the ovary or testes.[13] On the other hand, administration of thyroid hormone will result in regranulation of those pituitary cells with restoration of their normal metabolism, including the secretion of gonadotrophins. In short, the thyroid hormone is essential for the normal functioning of the anterior pituitary in producing gonadotrophic hormone(s).[14] In addition, thyroid may also influence the gonad directly through its influence upon cellular metabolism.

In view of these considerations, it certainly seems like more rational therapy to influence the clinically hypofunctioning ovary by means of its normal regulator, the anterior pituitary, through the administration of a nutritionally balanced diet and the thyroid hormone than by the use of substitute heterogenous gonadotrophins whose value is as yet unproved and whose effects at best are temporary and may even be gonadotoxic.

Our results with thyroid extract both in this study and in other cases clearly reveals that thyroid hormone still remains the endocrine preparation par excellence for the management of functional menstrual disorders. Of the 9 cases in this series which were eventually "salvaged," the successful therapeutic result in 8 was correlated with the use of thyroid, an adequate dietary

regime, or both. It should be emphasized that the basal metabolic rate is only a relative determination to be evaluated in the light of the patient's clinical picture. For example, Case 7 had a basal metabolic rate of +18 on three occasions, checked twice each time. Yet it was not until she was placed on 190 mg. (3 grains) of desiccated thyroid daily that she began to menstruate regularly, and eventually a secretory endometrium was found premenstrually.

From a clinical point of view, the evocation of antagonistic (antigonadotrophic?) substances *to equine gonadotrophin* is of great importance not only in realizing that subsequent therapy with equine gonadotrophin may be useless but also in explaining certain reactions to it. This subject has been discussed more fully in previous papers.[11] Allergic manifestations to equine gonadotrophin have been reported by several investigators, including Erving, et al.,[4] Bickers,[15] and Fluhman.[7] *These may occur in spite of negative skin tests.*

Summary

Twenty-two patients with clinically hypofunctional ovarian activity were studied. These comprised 3 cases of primary amenorrhea, 11 of secondary amenorrhea, 8 of oligomenorrhea, and one of cyclic anovulomenorrhea. Adjuvant therapy with equine gonatrophin was instituted in these cases.

This hormone failed to establish menstruation in three cases of primary amenorrhea.

Of the 11 cases of secondary amenorrhea, ovulation was apparently stimulated in two although the result in one was open to serious question. Only one patient continued to have regular menses.

In the 7 cases of oligomenorrhea, equine gonadotrophin apparently restored cyclic menses in one but failed to stimulate an ovulatory response in any.

In the one case of regular anovulomenorrhea, equine gonadotrophin was ineffectual.

Nine of these 22 patients were later "salvaged" with an adequate diet and, usually, thyroid extract.

Conclusions

1. Clinically, equine gonadotrophin proved to be a rather ineffectual stimulant to the abnormally functioning or hypofunctioning human ovary as far as the restoration of normal cyclic metabolism and the reappearance of regular menstrual rhythm was concerned.

2. Equine gonadotrophin produced similarly poor results in stimulating an ovulatory response in patients with clinically hypofunctioning or abnormally functioning ovaries.

3. The principle of heterogenous substitutive therapy with equine gonadotrophin may yield far greater harm than any temporary good. The possible harmful results of therapy with equine gonadotrophin are (a) a gonadotoxic effect on the ovary as evidence by abnormal stimulation or marked delay in appearance of the next menses, (b) development of antagonistic (antigonadotrophic?) substances with neutralization of subsequent injections of equine gonadotrophin, (c) development of allergic manifestations, which may be severe in spite of negative skin tests, (d) sensitization of the patient to other as yet unknown components of horse serum.

4. The principle of physiologic stimulative therapy by means of a nutritionally balanced diet and desiccated thyroid extract is far more rational and far more efficacious both on theoretical considerations and on the clinical results obtained.

The authors are indebted to Dr. H. C. Falk, Director of the Department of Gynecology of Harlem Hospital, for permission to carry out most of this work and to publish our findings.

Both preparations of equine gonadotrophin were supplied as Gonadogen, by Dr. G. F. Cartland of the Upjohn Company.

We are particularly grateful to Miss Sylvia Krause, Dietitian in charge of Special Diets at the Harlem Hospital, for her splendid help and cooperation.

This work was carried out for the main part while one of us (A. R. A.) was associated with the Department of Gynecology, Harlem Hospital, New York. Dr. Leathem's studies were begun while he was associated with the Department of Anatomy, College of Physicians and Surgeons, Columbia University, New York, and were continued at Rutgers University, New Brunswick, New Jersey.

References

1. Cole, H. H., and Hart, G. H.: Am. J. Physiol. **93**: 57, 1930.
2. Davis, M. E., and Koff, A. K.: Am. J. Obst. & Gynec. **36**: 183, 1938.
3. Davis, M. E.: J. Clin. Endocrinol. **3**: 517, 1943.
4. Erving, H. W., Sears, C., and Rock, J.: Am. J. Obst. & Gynec. **40**: 695, 1940.
5. Brewer, J., Jones, H. O., and Skiles, J. H.: J. A. M. A. **118**: 278, 1942.
6. Vogt, W. H., Jr., and Sexton, D. L.: Am. J. Obst. & Gynec. **48**: 81, 1941.
7. Emge, L.: In Discussion of paper by Fluhman: West. J. Surg. **48**: 63, 1940.
8. Hartman, C. G.: Bull. Johns Hopkins Hosp. **63**: 351, 1938.
9. Greenblatt, R. B.: Am. J. Obst. & Gynec. **42**: 983, 1941.
10. Geist, S. H., Gaines, J. A., and Salmon, V. J.: Am. J. Obst. & Gynec. **42**: 619, 1941.
11. a) Leathem, J. H., and Abarbanel, A. R.: J. Clin. Endocrinol. **3**: 206, 1943.
    b) Ibid.: West. J. Surg. **51**: 177, 1943.
12. Mason, K.: In Sex and Internal Secretions, ed. 2, Baltimore, 1939, Williams & Wilkins Co., Chap. XXII.
13. Sevringhaus, A. E.: In Sex and Internal Secretions, ed. 2, Baltimore, 1939, Williams & Wilkins Co., Chap. XIX.
14. Sevringhaus, A. E.: West. J. Surg. **50**: 371, 1942.
15. Bickers, W.: J. Clin. Endocrinol. **1**: 852, 1941.

1726 Eye Street, N.W.

A COMPARATIVE STUDY OF THE CLINICAL RESPONSES OF WOMEN WITH HYPOFUNCTIONING OVARIES TO TWO METHODS OF COMBINED GONADOTROPIC THERAPY*

C. D. Davis, M.D., and E. C. Hamblen, M.D., Durham, N. C.

(From the Endocrine Division of the Department of Obstetrics and Gynecology, Duke University School of Medicine and Duke Hospital)

A RECENT study by us,[1] which included data previously reported by other members of our group, has shown that the sequential and cyclic administration of equine and chorionic gonadotropins (one-two cyclic gonadotropic therapy) restores to a fertile status a significant number of women with hypofunctioning ovaries. The commercial availability of a product† which contains both pituitary synergist and chorionic gonadotropin (called hereafter SYN.) has suggested the likelihood that it may yield as effective therapy as the sequential and separate administration of equine and chorionic gonadotropins.‡ This communication is concerned with a comparative study of the two methods of treatment in a group of twenty-one patients.

*Parts of the expenses of these studies were defrayed by grants to one of us (E.C.H.) by the Research Council of Duke University, and by Parke, Davis and Co., Detroit, Mich.

†Synapoidin, Parke, Davis and Co., Detroit, Mich.

‡Equine gonadotropin: Anteron (Schering Corporation) and Gonadogen (Upjohn Company); chorionic gonadotropin: APL (Ayerst, McKenna and Harrison); and chorionic gonadotropin (Upjohn Company).

Selection of Patients

The twenty-one patients fell into four clinical categories: (1) those with deficient sexual maturation whose menarches had not occurred, four patients; (2) those with infrequent and/or scanty estrogenic bleeding, six patients; (3) those with prolonged and/or excessive estrogenic bleeding, five patients; and (4) those with presumed ovarian sterility associated with bleeding from immature progestational endometriums, six patients.

1. *Patients With Deficient Sexual Maturation Whose Menarches Had Not Occurred.*—All possessed striking hypoestrogenism. In none a definite diagnosis of hypopituitarism was made. Accordingly, the likelihood of an intrinsically ovarian etiology existed in all. The endocrine state of these patients was not relatable to organic or constitutional disease. Hypothyroidism, as an etiological factor, was eliminated by clinical studies, basal metabolic rates, and by preliminary treatment with desiccated thyroid gland of those patients in whom there was some evidence of hypothyroidism.

2. *Patients With Infrequent and/or Scanty Bleeding.*—Upon the basis of endometrial biopsies secured at the onsets of episodes of uterine bleeding, all of these patients were judged to have anovulatory ovarian failure, that is, they bled from interval or estrogenic endometriums. There was no evidence of hypoestrogenism.

No more definite statements of the etiology of the ovarian failure for this group of patients were possible than for the first group.

3. *Patients With Prolonged and/or Excessive Bleeding.*—In common with the patients of the second group, these patients were characterized by anovulatory ovarian failure without hypoestrogenism, that is, all bled from estrogenic or interval endometriums.

Similar to the patients of the first and second groups, no definite diagnoses of the etiology of the ovarian failure were possible; however, constitutional and organic gynecologic factors were excluded.

4. *Patients With Presumed Ovarian Sterility Associated With Bleeding From Immature Progestational Endometriums.*—We assumed that bleeding from immature progestational endometriums by these patients was significant of endocrine deficiency since no other demonstrable causes of sterility were found in careful diagnostic surveys of these wives and their husbands. We considered two likely mechanisms: (1) ovulations might have occurred and, yet, the immature progestational endometriums might have prevented nidation of any fertilized ova, that is, the existence of hypoprogestinism without anovulatory ovarian failure; and (2) ovulations might not have occurred and, instead, ova were imprisoned in follicles, the granulosa of which subsequently became luteinized providing low progestin stimulation of the endometrium, that is, the existence of anovulatory ovarian failure and hypoprogestinism. Acceptance of the latter of these two mechanisms justified the use of gonadotropic therapy.

No more definite causes for the ovarian failure of this group of patients were ascribable than for that of the patients of the third group.

All of the patients of this group experienced cyclic and essentially normal bleeding with regard to duration and amount. Therefore, they stand in striking contrast to the patients of the second and third groups.

Method of Study

The clinical studies of all of the patients embraced endocrine and gynecologic surveys, determinations of basal metabolic rates, and roentgenograms of the sella turcica. Roentgenologic estimations of osseous age were made in those patients with deficient sexual maturation and those 20 years of age or less. Endometrial biopsies were done at the onset of episodes of bleeding, prior to, during, and frequently after therapy. Because of the hypoestrogenism of the patients of the first group, initial biopsies were omitted. At least two consecutive episodes of bleeding were biopsied, if possible, prior to treatment of the patients of the second, third, and fourth groups. This seemed advisable lest chance variations might be classed as ovarian habits of a patient.

All biopsy material, after fixation, mounting, and staining, was studied and classified by one of us (E.C.H.). This practice has been followed in previous studies and, thereby, has permitted a uniformity and continuity of interpretation of endometrial responses.

Details of the special methods of handling these groups of patients were given in a previous communication.[1] These included use of estrogens for hemostasis (in prolonged and/or excessive bleeding), use of estrogens for sexual maturation (in deficient sexual maturation), use of cyclic estrogen therapy for cycle regulation (patients of first, second,

and third groups), test of endometrial receptivity to progesterone therapy (patients of first, second, and third groups) and salvage test (patients of first, second, and third groups).

Therapeutic Schedules

The schedules for *hemostasis, cyclic estrogen therapy,* and for *cyclic estrogen-progesterone* therapy were given in a previous communication.[1]

One-Two Cyclic Gonadotropic Therapy.—Prior to initiating one-two cyclic gonadotropic therapy, all patients were skin tested with the equine gonadotropin preparation to ascertain possible allergy. Skin tests were repeated before each projected series of therapy. Patients with definite allergy were not treated.

Gonadotropins were given intramuscularly and daily. Therapy was initiated on the fifth day of the cycle. From the fifth through the fourteenth days of the cycle, patients received intramuscularly and daily 400 international units of equine gonadotropin. From the fifteenth through the twenty-fourth days of the cycle, patients received intramuscularly and daily 500 international units of chorionic gonadotropin. When bleeding occurred before treatment was completed, injections were discontinued.

As a rule, and out of respect for possible antibody or antihormonal phenomena, series of one-two cyclic gonadotropic therapy were not given in sequence but, instead, several months were allowed to elapse between any two series of therapy.

SYN. Therapy.—Two schedules employing the preparation of pituitary synergist and chorionic gonadotropin were used: (1) 10 SYN., and (2) 20 SYN.

10 SYN. embraced the daily and intramuscular administration of 30 "synergy units" of SYN. from the fifth through the fourteenth days of the cycle.

20 SYN. embraced the daily intramuscular administration of 30 "synergy units" of SYN. from the fifth through the twenty-fourth days of the cycle.

Patients were skin tested with SYN. prior to each series of therapy in order to avoid allergic phenomena.

Clinical Data and Results

1. *Patients With Deficient Sexual Maturation Whose Menarches Had Not Occurred.*—The ages of these four patients ranged from 16 to 19 years.

Three of the four patients received a total of four series of 10 SYN. therapy. All yielded hypoestrogenic or atrophic endometriums at the onsets of bleeding which followed therapy.

Three of the four patients received a total of four series of 20 SYN. therapy. All yielded hypoestrogenic or atrophic endometriums at the onsets of bleeding which followed therapy.

The four patients received a total of five series of one-two cyclic gonadotropic therapy. All patients yielded hypoestrogenic or atrophic endometriums at the conclusion of therapy.

2. *Patients With Infrequent and/or Scanty Bleeding.*—The ages of these six patients ranged from 17 to 35 years. Their menarcheal ages ranged from 11 to 15 years.

Two were single and four married. Two of the married patients were nulliparous, one had had twins, and one an abortion.

When first seen, the elapsed time between the last bleedings of these patients varied from three to thirteen months.

Two of the six patients received a series of 10 SYN. therapy. Both patients yielded estrogenic endometriums at bleeding following the conclusion of therapy (one normal estrogenic and one hypoestrogenic endometrium).

Five of the six patients received a total of six series of 20 SYN. therapy. Four patients yielded estrogenic endometriums (two normal estrogenic and two hypoestrogenic) after their therapy. The fifth patient, who was given two series of therapy, yielded an immature progestational and normal estrogenic endometrium.

All six patients received one-two cyclic gonadotropin therapy. A total of seven series was given. The patient who gave an immature progestational response to 20 SYN. therapy yielded a full-blown progestational endometrium after one-two cyclic gonadotropic therapy. The other five patients yielded three normal estrogenic and three hypoestrogenic endometriums after therapy.

3. *Patients With Prolonged and/or Excessive Bleeding.*—The ages of the five patients ranged from 16 to 31 years. Their menarcheal ages ranged from 12 to 15 years.

Three of these patients were single and two married. One of the married patients was nulliparous and one had had an abortion.

Four of the five patients when first seen had had episodes of prolonged bleeding which ranged from twenty-three days to twenty months in duration. One had had excessive bleeding of six days in duration. The severity of the uterine hemorrhages of these patients is indicated by their hemoglobin values, which ranged from 45 to 81 per cent, with an average value of 61 per cent.

Three of these patients received a total of three series of 10 SYN. therapy. Following therapy, two patients gave normal estrogenic endometriums and one a hypoestrogenic endometrium.

All five patients received 20 SYN. therapy for a total of five series. Two patients gave progestational endometriums at the conclusion of therapy: one full-blown progestational endometrium and one immature progestational endometrium. The other three yielded normal estrogenic endometriums at the end of therapy.

All five patients received one-two cyclic gonadotropic therapy for a total of five series. Four of the five patients yielded full-blown progestational endometriums and one a normal estrogenic endometrium at the conclusion of treatment. Both of the patients who gave positive responses to 20 SYN. therapy yielded progestational responses following one-two cyclic gonadotropic therapy.

4. *Patients With Presumed Ovarian Sterility Associated With Bleeding From Immature Progestational Endometriums.*—The ages of these six patients ranged from 23 to 29 years. Their menarcheal ages ranged from 11 to 16 years.

All were married: five were nulliparous and one had had one term delivery.

The bleeding of these patients was cyclic and of normal amount and duration.

Five of the six patients received 10 SYN. therapy, one series to a patient. Three patients gave immature progestational endometriums following treatment, one a full-blown progestational endometrium, and one supplied insufficient endometrium for diagnosis.

One of the six patients received 20 SYN. therapy. Following therapy, a full-blown progestational endometrium was found.

Three of the six patients were treated with one-two cyclic gonadotropic therapy, one series to a patient. Two yielded immature progestational endometriums following therapy and one a full-blown progestational endometrium.

None of these six patients became pregnant in relation to SYN. or one-two cyclic gonadotropic therapy.

Discussion

The initial clinical report on the experimental use of SYN. by Mazer and Ravetz[2] established its gonadotropic properties. Following intensive therapy prior to laparotomy, these observers found multiple corpora lutea together with evidences of overstimulation in the ovaries of twenty out of twenty-three women who were treated. Two facts stood out from this study: (1) their patients apparently were characterized by normally reactive ovaries and their responses were augmentational ones typified by multiple corpora lutea; (2) the apparent overstimulation observed in these ovaries aroused the questions as to whether or not physiologically normal ova were discharged and whether or not normally functioning corpora lutea resulted.

Subsequently other clinical studies employing SYN. appeared.[3-5] These included ovarian studies after preoperative administration of SYN. and studies which described applications to the treatment of hypoovarian states. None of these studies has established any definite therapeutic application of SYN.

Our selection of dosage schedule was based fundamentally on arbitrary grounds. In a previous report[6] of our results with SYN. in the treatment of males with seminal inadequacy, we encountered disagreeable constitutional and local reactions when relatively large doses of SYN. were used. Accordingly, we chose a daily dose of 30 "synergy units" (or 2 c.c. of the commercial preparation). This amount appeared to be about all that the average patient could tolerate without too frequent untoward reactions.

Two therapeutic schedules employing SYN. were used. One of these emphasized the follicle-stimulating possibilities of SYN., embracing its adminis-

tration from the fifth through the fourteenth days of the cycle. The other schedule took into account probable follicle-stimulating and luteinizing functions of SYN., being characterized by its administration from the fifth through the twenty-fourth days of the cycle.

Despite the fact that no patient was treated with SYN. who gave a positive skin test prior to a series of anticipated therapy—and, incidentally, a number of patients who otherwise might have been treated with this preparation were disqualified on these grounds—three of the twenty-one patients experienced rather severe local and constitutional reactions. One patient on the thirteenth and fourteenth days of therapy experienced severe systemic reaction, characterized by fever, general malaise, and impossibility of moving the arm because of pain. Therapy was promptly discontinued. Endometrial biopsy subsequently yielded a full-blown progestational endometrium. Another patient on the seventh day of therapy had a moderately severe general systemic reaction. A third patient required discontinuation of treatment on the tenth day because of severe local reaction at the site of injection. These reactions to SYN. should be contrasted with the infrequency of reactions during one-two cyclic gonadotropic therapy.[1]

The endometrial responses to SYN. and one-two cyclic gonadotropic therapy of the patients with deficient sexual maturation were essentially the same. No patient gave any evidence that her ovaries were stimulated to full physiologic activity. These findings are in line with those reported in a larger series of similar patients treated with one-two cyclic gonadotropic therapy.[1]

The endometrial responses of the patients with infrequent and/or scanty bleeding to both forms of treatment were in fairly good agreement. Only one of the six patients responded to gonadotropic therapy and she responded to both 20 SYN. and one-two cyclic gonadotropic therapy. A full-blown progestational endometrium followed one-two cyclic gonadotropic therapy, whereas an immature progestational endometrium followed 20 SYN. therapy.

The endometrial responses of the five patients with prolonged and/or excessive uterine bleeding are consistent. Two of the patients who received 20 SYN. therapy yielded progestational endometriums, one giving a full-blown and one an immature progestational response. These same two patients also responded to one-two cyclic gonadotropic therapy, both giving full-blown progestational responses. Two other patients who failed to respond to SYN. therapy gave full-blown progestational responses to one-two cyclic gonadotropic therapy.

The results of the treatment of six patients with presumed ovarian sterility in association with bleeding from immature progestational endometriums were essentially the same for both systems of gonadotropic therapy. In no instance did the therapy reverse the endometrial pattern from a progestational to an estrogenic type. In one of four patients treated with 10 SYN. therapy, the endometrium was advanced to a full-blown progestational type. In the one patient treated with 20 SYN. therapy, the endometrium was advanced to a full-blown progestational status. In one of the three patients treated with one-two cyclic gonadotropic therapy, the endometrium was advanced to a full-blown progestational type. Since no pregnancies have occurred during SYN. therapy, a definite statement cannot be made that physiologically normal responses are elicited in the ovaries. We are of the opinion, however, that when a larger series of patients with sterility is treated with SYN., pregnancies may be obtained.

The data secured from the treatment of patients with infrequent and/or scanty bleeding and with prolonged and/or excessive bleeding indicate that the effective method of administering SYN. is the 20 SYN. therapy schedule, that is, its administration from the fifth through the twenty-fourth days of the cycle. Apparently, dosage increases are not necessary. These would produce, probably, more serious responses. It is apparent, however, that when these two groups of patients are considered, the use of SYN. therapy, although producing favorable responses, does not afford as high an incidence of these responses as the single and sequential administration of equine and chorionic gonadotropins.

Summary and Conclusion

The clinical responses of twenty-one patients (four with deficient sexual maturation, six with infrequent and/or scanty estrogenic bleeding, five with prolonged and/or excessive estrogenic uterine bleeding, and six with presumed ovarian sterility associated with bleeding from immature progestational endometrium) to two systems of gonadotropic therapy were subjected to comparative study. The primary criterion for an evaluation of these responses was a study of endometrial biopsies taken prior to and following treatment. One method of therapy employed the single and sequential administration of equine and chorionic gonadotropins—so-called one-two cyclic gonadotropic therapy. The other method of therapy employed a preparation which contained a mixture of "pituitary synergist" and chorionic gonadotropin. Positive responses followed the latter therapy only when it was given for twenty days, from the fifth through the twenty-fourth days of the cycle.

None of the patients with deficient sexual maturation responded to either therapy. Patients with infrequent and/or scanty estrogenic bleeding and those with prolonged and/or excessive estrogenic bleeding responded to both therapies. More positive responses, however, were associated with one-two cyclic gonadotropic therapy. No pregnancies were associated with either therapy in the group of patients with presumed ovarian sterility associated with bleeding from immature progestational endometriums.

These conclusions appear warranted:

1. Cyclic therapy with a preparation containing "pituitary synergist" and chorionic gonadotropin (30 "synergy units" intramuscularly and daily from the fifth through the twenty-fourth days of the cycle) may produce progestational endometriums in patients experiencing various grades of estrogenic bleeding.

2. This therapy, however, yields a lower incidence of positive responses than so-called one-two cyclic gonadotropic therapy, which employs singly and sequentially equine and chorionic gonadotropins, but a higher incidence of untoward reactions.

References

1. Hamblen, E. C., and Davis, C. D.: Am. J. Obst. & Gynec. 50: 137, 1945.
2. Mazer, C., and Ravetz, E.: Am. J. Obst. & Gynec. 41: 474, 1941.
3. Greenblatt, R. B.: Am. J. Obst. & Gynec. 42: 983, 1941.
4. Greenblatt, R. B., and Pund, E. R.: South. M. J. 34: 730, 1941.
5. Gray, L. A.: Am. J. Obst. & Gynec. 43: 387, 1942.
6. Davis, C. D., Madden, J. H. M., and Hamblen, E. C.: J. Clin. Endocrinol. 3: 357, 1943.

CARCINOMA OF THE CERVIX COMPLICATED BY PREGNANCY

J. ROBERT WILLSON, M.S., M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-in Hospital)

BECAUSE carcinoma of the cervix is rare in pregnancy, it usually is not considered in the differential diagnosis of bleeding, and the lesion may not be discovered until it has progressed to a stage at which all hope for a cure is lost. The diagnosis of carcinoma should present no difficulty if the possibility of its existence occurs to the physician. Examination, which must of necessity include visualization of the cervix, is of utmost importance; the final conclusive proof, however, depends upon the microscopic examination of tissue removed from the suspicious area on the cervix.

Danforth,[1] from a series of published reports, concluded that the incidence of cervical carcinoma complicating pregnancy is only 0.0321 per cent. This low figure is not surprising when one considers that the incidence of cancer of the cervix in the nonpregnant is also low in the younger age groups into which most of the childbearing women fall; thus malignancy and pregnancy combined are limited to only a small group of those who are potential candidates for either condition.

Since 1931, six patients with carcinoma of the cervix and pregnancy have been treated at the Chicago Lying-in Hospital (Tables I and II). Of these, two were referred to the hospital for treatment after the diagnosis had been made elsewhere. The remaining four lesions were discovered among our own patients. During this same period of time a total of 39,719 patients have been delivered; thus the incidence of cervical carcinoma in our patients is one in each 6,620 deliveries or 0.015 per cent. All the lesions were of squamous-cell origin with the exception of that in Patient 3, which was adenocarcinoma.

Diagnosis

The diagnosis of early carcinoma of the cervix during pregnancy can be made only if the possibility of its existence is considered. Bleeding which appears during early pregnancy and which persists for more than one week despite bed rest may be due to a malignancy. In such cases it is imperative that a pelvic examination be made (1) to establish the diagnosis of pregnancy, and (2) to determine the cause of the bleeding. In most instances, bloody discharge during the first trimester of pregnancy is due to threatened abortion. In the majority of these cases, however, the bleeding will either stop after a few days' rest in bed or the products of conception will be expelled from the uterus. Abortion usually is accompanied by cramps due to uterine contraction. While examination may hasten or even precipitate the emptying of the uterus in such a case, prolonged observation of pregnant patients who are bleeding from an undetermined site is dangerous. Sterile vaginal examination after one week of bleeding which continues despite complete bed rest is a necessity. The history of a missed menstrual period, severe pain, and bleeding, which usually characterizes an extrauterine pregnancy, calls for a complete and immediate investigation.

TABLE I

PATIENT	DURATION OF PREGNANCY (WEEKS)	SIGNS OF CARCINOMA AND DURATION	SIZE OF LESION AND CLINICAL CLASSIFICATION (SCHMITZ) AT FIRST EXAMINATION	INTERVAL FROM FIRST SIGN TO FIRST TREATMENT
1. Age 39 Para iii	28	No signs. Suspicious lesion found on speculum examination	Small. Confined to posterior lip II	6 days. No delay
2. Age 30 Para v	2½ months postpartum	Painless irregular bleeding 12 months	Entire vaginal vault replaced by neoplasm IV	12 months. Patient did not report to her doctor until late in pregnancy—was not examined
3. Age 42 Para xi	28	No signs. Suspicious lesion found on speculum examination	Entire anterior lip indurated and neoplastic II	27 days
4. Age 32 Para v	38	Postcoital bleeding	Posterior cervical lip indurated and neoplastic II	4 months. Examination for postcoital bleeding revealed no cervical lesion. Biopsy at delivery revealed only "squamous metaplasia"—not taken from area of cancer
5. Age 27 Para iv	6 weeks postpartum	Painless bleeding 6 weeks	Lesion involving both cervical lips II	Refused treatment
6. Age 38 Para viii	28	Painless bleeding 6 months	Entire anterior lip involved. Two nodules invesicovaginal septum IV	6 months. Patient did not report for examination

There are no subjective symptoms in the early case of carcinoma of the cervix. The signs during pregnancy are exactly like those which characterize the same lesion in the nonpregnant uterus: abnormal discharge or bleeding which, characteristically, is painless, irregular, progressive in amount, and prone to follow trauma. Pain, weight loss, and palpable extension, all appear late in the course of the disease and need not be considered in diagnosing the early lesion.

The pelvic examination to determine the cause of persistent bleeding must be carried out in a systematic manner. The external genitalia are first inspected and palpated, following which a careful digital exploration of the vagina is made. Early malignant areas on the cervix are characterized by induration or irregularity, which can sometimes be more readily felt than seen. After the entire cervix has been carefully palpated and the diagnosis of pregnancy confirmed, the vagina and cervix must be visualized through a speculum. This is one of the most important steps in the entire examination. Any suspicious area of induration or any cervical lesion which bleeds may be malignant and demands more complete investigation. The diagnosis of carcinoma must be made or at least confirmed by microscopic examination of adequate amounts of tissue taken from the suspected area. Such biopsies may be taken either in the outpatient with a suitable punch, or by excision in the hospital. Only in this way will the presence of an early malignancy be discovered.

It is a generally accepted rule that bleeding in late pregnancy should be

investigated in an effort to rule out placenta previa or abruptio placentae as a cause; at the time of the sterile vaginal examination, the practice of visualization of the cervix is a routine. Adequate biopsy of suspicious cervical lesions, especially of the site of the bleeding, may reveal an unsuspected malignancy. Patient 5 (Table I) was admitted to the hospital at thirty-four weeks' gestation, complaining of profuse painless vaginal bleeding. The placental edge was palpated and an intraovular bag inserted. There was no unusual bleeding during the hospitalization but after discharge the patient noted daily spotting. At the first return visit both cervical lips were involved in a malignant lesion which probably was present at the time of delivery. Had this patient not had a placenta previa as an obvious cause of bleeding, the malignancy probably would have been discovered when the examination was made.

The importance of an accurate pathologic diagnosis on the tissue removed cannot be overemphasized. Not uncommonly, cervicitis or areas of decidual reaction on the cervix during pregnancy may be everted, friable, and bleed freely upon manipulation. Grossly, such lesions cannot be differentiated from carcinoma. The microscopic changes in the pregnant cervix may likewise suggest that a malignant change has occurred. Hofbauer[2] described a marked proliferation and hyperplasia of the cervical epithelium during pregnancy, characterized by downgrowth of masses of epithelial cells beneath a normal layer of columnar epithelium, into the gland lumina, or beneath normal squamous epithelium. There may be noted a distinct variation in size and shape of the individual cells, mitotic figures, and vacuolization in the newly formed masses. In the cases in which the downgrowth is marked, difficulty may be encountered in differentiating these normal changes from malignancy. The important features of the normal proliferation which distinguish it from carcinoma are: the regularity of the mitoses, the minor changes in size and shape of cells, and the consistently intact basement membrane. If the lesion is found to be benign, it should not be treated during pregnancy. Such changes are part of the normal course of events and cannot be healed until the pregnancy terminates, after which reversion is in most cases spontaneous. Overly enthusiastic treatment of this common lesion might result in scarring and abnormal dilatation of the cervix in labor.

If the microscopic diagnosis is questionable, the patient should not be subjected to intense irradiation therapy which may destroy the fetus and permanently injure the mother. Before the initiation of treatment in such a case, examination of the sections by several competent gynecologic pathologists is essential.

The following two cases, one treated for carcinoma and one observed, illustrate this point:

CASE 1.—C. S., aged 24 years, gravida ii, para i. This patient was first seen in our clinic in February, 1932. At that examination there was noted eversion of the cervix and papillary outgrowths on both lips. Because of a microscopic diagnosis of adenocarcinoma, a plaque containing 200 mg. of radium was applied against the cervix for a total dosage of 3,800 mg. hours, and seven weeks later a cesarean section and modified Wertheim hysterectomy were done. Several competent gynecologic pathologsts who examined the sections were all of the opinion that the lesion was not malignant.

Although the patient is still alive and apparently well, she developed a moderate irradiation proctitis, much pelvic pain, was completely castrated, and was subjected to an operative procedure with a mortality rate of 14 per cent, all for the treatment of a benign cervical lesion.

TABLE II

PATIENT	DURATION OF PREGNANCY AT TIME OF DIAGNOSIS	INITIAL THERAPY	METHOD OF TERMINATING PREGNANCY	TREATMENT FOR CARCINOMA			COMPLICATIONS OF TREATMENT	SURVIVAL
				SURGERY	X-RAY DEPTH DOSE TO EACH PARAMETRIUM	RADIUM (MG. HR.)		
1. 188041	28 weeks	Radium in canal and to surface	Cesarean section 2 weeks after radium	Total hysterectomy, bilateral salpingo-oophorectomy	4630 r. 2 series	3000 before delivery	None	Alive 80 months
2. 223781	2½ months postpartum	Radium	Vaginal—without treatment	None	2700 r.	5126 after delivery	None	Dead 14 months
3. 63977	28 weeks	Radium to surface and in canal	Spontaneous delivery 2 weeks after radium	None	4200 r. (skin) Aug., 1932, 4900 r. (skin) Feb., 1937	3100	None	Dead 89 months
4. 154145	38 weeks	Radium	Spontaneous vaginal delivery	None	3200 r.	4900 after delivery	Irradiation proctitis	Alive 23 months
5. 92943	6 weeks postpartum		Vaginal—bag induction for placenta previa	None	None	None		Dead 20 months
6. 326686	28 weeks	Radium to vagina and cervix	Cesarean hysterectomy 6 weeks after radium	None	3000 r.	Cervix 3540. Vagina (interstitial) 1882 before delivery	None	Alive 10 months

CASE 2.—T. T., aged 33 years, gravida i, para 0. At the time of the initial examination on July 8, 1935, when the patient was about fourteen weeks pregnant, the cervix was described as showing "decidual reaction." On Oct. 21, 1938, slight vaginal bleeding occurred, and a benign cervical polyp was removed. There was no further bleeding until Feb. 8, 1939, at which time the patient was forty-one weeks pregnant. There was noted a friable everted lesion on the cervix which grossly was suggestive of malignancy. Because of an advancing pre-eclampsia, the pregnancy was terminated on Feb. 10, 1939 (forty-one weeks), by laparotrachelotomy which was preceded by a cervical biopsy. The tissue removed was reported to be adenocarcinoma; however, after the sections were reviewed by several members of our staff, it was decided that the lesion was benign. Without treatment the cervix healed and has been normal since. Had the original diagnosis of carcinoma been accepted without question, this patient would undoubtedly have been subjected to a course of irradiation which would have been followed by castration and possibly injury to normal structures.

In another case (No. 4, Table I) delay in treating a carcinoma resulted from an inadequate biopsy. This patient had complained of postcoital bleeding on her first visit to one of our outlying clinics but no cervical lesion was noted on examination. She was admitted to the hospital at thirty-eight weeks' gestation with painless vaginal bleeding. At the time of examination an indurated area noted in the posterior cervical lip was biopsied. The initial report was "squamous metaplasia" and it was not until the second postpartum visit that tissue showing carcinoma was submitted to the pathologist. Thus, the initiation of treatment was delayed by several weeks.

Prognosis

The prognosis for carcinoma of the cervix discovered during pregnancy and properly treated seems to be at least as good as that in the nonpregnant individual; five of Emge's[4] six cases and three of the four cases reported by Richman and Goodfriend[5] survived more than five years (of the latter group, one for six years, one for eight years, and the third for five years; the last, however, had extensive involvement at that time). Maino and Mussey[6] reported 30 per cent five-year survival in twenty patients treated at the Mayo Clinic.

The five-year survival rate for the cases presented here is 50 per cent for those who are eligible for that consideration. Since one of these four patients refused treatment, two, or 67 per cent of those treated, lived more than five years after the initiation of therapy.

This survival rate is not surprising since usually the diagnosis should be made early in the course of the disease. A far-advanced cervical lesion with a large infected fungating tumor mass will, in most instances, preclude conception, but an early lesion may not. The latter type should be discovered at the time of the initial prenatal visit if a complete examination is made.

Two patients in our series (Nos. 1 and 3, Table I) had no symptoms referable to the carcinoma; both were discovered at the time of the initial pelvic examination and one (No. 1) had the smallest lesion found. The other lesion was an adenocarcinoma, in which usually the first sign may be somewhat delayed. This lesion involved only the anterior lip. The first patient is alive and well without evidence of malignancy after six years, and the second survived almost seven and one-half years but died of carcinoma (Table II). The latter was undertreated according to our present knowledge of the amount of irradiation necessary to eradicate carcinoma.

If the tumor appears during the course of the pregnancy, the physician usually is warned by the appearance either of an abnormal discharge or of bleeding which typically is painless, irregular, progressive in amount, and prone to follow trauma. The presence of vaginal bleeding or discharge demands a complete pelvic examination to establish the cause.

The belief that the rate of growth of carcinoma of the cervix is increased

by the pregnancy has not been substantiated. Peller,[3] after demonstrating that the relative number of carcinomas occurring during pregnancy was significantly less than the number occurring in similar age groups in the nonpregnant, concluded that pregnancy not only increases the resistance to cancer, but raises the average age of its occurrence and retards its progress.

In addition to the belief that the increased blood and lymph circulation increases the opportunities for spread of the malignancy, it has been suggested that the marked rise in the estrogenic hormones during pregnancy may be a factor both in the production and extension of the disease. This latter supposition is based upon the fact that cancer may be produced in certain susceptible laboratory animals by stimulation with large dosages of estrogens. Emge,[4] studying rats which were particularly free from breast and genital cancer, carried them through a series of rapidly recurring pregnancies in an effort to produce the maximum stimulation of breast and genital tissue. No malignancies developed in the group of animals and he concluded that the role of the estrogenic hormones in the production of cancer is secondary to, and limited by, the hereditary factors.

The prognosis for those patients who have had no prenatal care or in whom the warning signs have been ignored may be less favorable. Patient 2 in this series (Table II) had had symptoms for twelve months before we first saw her two and one-half months post partum. Although irregular bleeding was noted early in pregnancy and continued throughout, this cardinal sign was ignored both by patient and physician. The former delayed several months in visiting her doctor, and the latter likewise wasted time by treating the bleeding "conservatively" without examination. Eradication of the neoplasm, which when diagnosed almost filled the pelvis, was impossible, and the patient survived only fourteen months after treatment which might have completely destroyed a smaller lesion. Since the advanced lesions usually are grossly infected and the carcinomatous tissue is friable and bleeds readily, the hazards from the generalized spread of infection and from hemorrhage incident to the trauma of labor are increased.

The fetal prognosis depends, of course, primarily upon the stage of the pregnancy at the time the carcinoma is discovered; the initiation of therapy, either irradiation or surgical, before the period of viability must, of necessity, sacrifice the infant. If the lesion is discovered after the period of viability has been reached, the plan of treatment may include procedures designed to save the baby unless such a method may decrease the chance for destruction of the neoplasm.

Treatment

The treatment of carcinoma during pregnancy is directed toward (1) destroying the malignant lesion and (2) reducing the hazards to the patient from infection and hemorrhage. Because of the small number of cases that have been observed, there is no conclusive weight of evidence pointing to any one method of treatment as being the most effective in accomplishing these aims. There are, however, certain facts which may well be considered whenever this condition is encountered.

Type of Treatment.—It is generally conceded that in most instances cervical cancer is best treated by a combination of radium and deep x-ray therapy. Since this method offers the best prognosis for the nonpregnant patient, there seems to be no reason for advocating, during pregnancy, radical surgical procedures de-

signed to remove the malignancy. The possible exception is the extremely early lesion confined to a small area on the cervix.

The amount of irradiation necessary to destroy the lesion is comparable to that in the absence of pregnancy. The presence of the pregnancy, however, may require an alteration in the routine of administration. The total amount of deep x-ray therapy should be an amount sufficient to deliver 3,000 r. to each parametrial area. This may be given through two anterior and two posterior lower abdominal portals. Occasionally, lateral portals are used. The total radium dosage should approximate 5,000 mg. hours, of which one-third is delivered to the body of the uterus and two-thirds to the cervix and surrounding parametrium. Patient 3 (Table II), when first examined, had been free from symptoms and had a lesion confined to one lip of the cervix. The initial deep x-ray therapy (1932) consisted of a total skin dosage of only 4,200 r. This, plus the 3,100 mg. hours of radium, retarded the growth of the neoplasm until 1937 at which time extension was first noted. Although further therapy was then given, the patient died of carcinoma. While it is impossible to state with any degree of certainty, it seems probable that adequate initial treatment might have eradicated the lesion.

Postirradiation pelvic lymphadenectomy as suggested by Taussig[11] for the treatment of early cervical cancer may improve the results over those with x-ray and radium alone. If it is true that lymphatic extension is hastened because of the pregnancy, the glands should be involved at an earlier stage than in the nonpregnant patient, and failure to cure early lesions may be the result of small foci in the lymph nodes which escaped destruction by the x-ray. We intend to make this addition to the treatment in the future.

Hemorrhage.—One of the hazards of delivery from below is bleeding. If the lesion is extensive and involves the greater part of the cervix, dilatation will not occur, but the friable vascular tissue may tear in all directions, resulting in exsanguinating hemorrhage. In the face of such a lesion, abdominal delivery is definitely indicated. Three of the patients delivered by us were delivered vaginally. In all, the lesion was relatively small and no unusual hemorrhage was encountered.

Infection.—While the danger from hemorrhage is lessened by cesarean section, that from infection is increased. A sloughing cervical lesion is always infected, commonly with streptococci. Through the placental site and the uterine wound, invasion of the organisms directly to the blood stream and peritoneal cavity may occur. If the lesion is fungating and infected, cesarean subtotal hysterectomy is the safest procedure. The argument that the cervical stump is a less advantageous place from which to irradiate the pelvis is not upheld by statistics on the treatment of stump cancer, which indicate that the results of treating this condition are better than when the uterine corpus is present.[7-10]

The administration of the sulfonamides by mouth pre- and postoperatively undoubtedly will reduce the danger from infection. As in other operative procedures, however, these drugs cannot be expected to compensate for poor technique and faulty judgment. Every effort to reduce infection in the local lesion prior to operation should be made.

The Fetus

While the life of the fetus is important, it cannot, in most instances, be weighed against that of the mother. During early pregnancy there can be

no question but that definitive therapy directed toward destroying the carcinoma be instituted as soon after the diagnosis is established as is possible. If the lesion is discovered after the period of presumed viability has been reached, little except advancement of the lesion can be gained by withholding treatment. However, should the lesion be far advanced with complete infiltration of the vaginal vault and pelvis so that no possible hope for cure exists, the pregnancy may be allowed to continue until a time at which there seems to be little question but that the infant will survive.

At the borderline, when a delay of one or two weeks may bring the baby to viability, a temporary delay in instituting treatment may be permissible. A more logical procedure in such cases, however, is to apply radium to the cervix and possibly even in the cervical canal as an initial step before the uterus is emptied. This procedure was carried out in Cases 1, 3, and 6, and in all, after a delay of from two to six weeks, a living baby was born.

If external irradiation is given over the uterus during early pregnancy, and abortion does not follow, fetal abnormalities occur in a high percentage of cases.[12] Microcephalic idiocy has been the defect most commonly noted. Murphy advises artificial interruption of any pregnancy which continues after irradiation.

Summary of Treatment

First Trimester.—X-ray therapy should be started as soon as the diagnosis is established. In most instances, abortion occurs during the third week of the treatment. Should this not occur or should it be incomplete, curettage may be carried out with little danger after the size of the lesion and infection in the cervix have been reduced by the irradiation. The external irradiation is carried to a calculated dosage of 3,000 r. to each parametrium and is followed by radium insertion after the uterus is empty. The total radium dosage consists of at least 5,000 mg. hours, of which one-third is delivered to the uterus and two-thirds to the cervix and surrounding parametrium.

Second Trimester.—Early in the second trimester, treatment like that described above may be initiated. The interruption of pregnancy is less consistent, however, and effective irradiation of the pelvis is diminished due to the increased size of the uterus.

During the late second trimester, an initial surface interstitial and/or intracervical application of radium may be followed, after the reaction has subsided, by cesarean hysterectomy. A complete course of x-ray therapy, which may be started as soon as the wound is healed, is followed by the intrauterine application of radium to complete the total dosage. Delivery from below is contraindicated unless the lesion is very small.

Third Trimester.—Treatment during the third trimester is much like that during the latter part of the second. There is no reason for delaying the initial treatment of the cancer. The larger the baby the more dangerous becomes vaginal delivery, and the closer to term the more apt are local manipulations to precipitate labor. In the majority of cases, abdominal delivery is the method of choice. Patient 3 was delivered vaginally two weeks after the radium implantation. She was admitted in active labor with the cervix well dilated. Since the infant was small, delivery from below was allowed. Patient 4 was examined near term for bleeding, and since she was in labor and because the diagnosis of carcinoma had not been established, delivery from below was permitted. The diagnosis of carcinoma was not made in Patient 5.

Summary

The existence of pregnancy and carcinoma of the cervix together is unusual and presents a difficult problem in therapy, but an unusual opportunity to treat early lesions may present itself. The prompt and thorough investigation of bleeding during pregnancy is an important step in diagnosing the condition and may be responsible for saving the life of the patient. In most instances, radical surgical procedures have no place in treatment since the results from combined irradiation are equally as good. A high fetal mortality is inevitable since it usually is unwise to resort to methods of treatment which attempt to preserve the fetus but which may decrease the chances for cure of the neoplasm.

Of the three patients in this series eligible for consideration, two (67 per cent) survived longer than five years after treatment; only one, however, is free from evidence of carcinoma.

References

1. Danforth, W. C.: Am. J. Obst. & Gynec. 34: 365, 1937.
2. Hofbauer, J.: Am. J. Obst. & Gynec. 25: 779, 1933.
3. Peller, S.: Wien. klin. Wchnschr. 38: 892, 1925.
4. Emge, L. A.: Am. J. Obst. & Gynec. 28: 682, 1934.
5. Richman, S., and Goodfriend, M. J.: Am. J. Roentgenol. 48: 677, 1942.
6. Maino, C. R., and Mussey, R. D.: Am. J. Obst. & Gynec. 47: 229, 1944.
7. Scheffey, L. C.: J. A. M. A. 107: 837, 1936.
8. Ward, G. G.: Am. J. Obst. & Gynec. 41: 660, 1941.
9. Behney, C. A.: Am. J. Obst. & Gynec. 40: 780, 1940.
10. Watkins, R. E.: Northwest. Med. 40: 172, 1941.
11. Taussig, F. J.: Am. J. Roentgenol. 45: 813, 1941.
12. Murphy, D. P.: Am. J. Obst. & Gynec. 18: 179, 1929.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE*

Robert M. Mitchell, M.D.,† and Roy W. Mohler, M.D., Sc.D.,‡
Philadelphia, Pa.
(From the Lying-In Division of the Pennsylvania Hospital)

THE objective of this article is threefold: (1) to submit a case report of primary carcinoma of the Fallopian tube discovered on routine microscopic examination of segments removed at the time of an elective cesarean section, (2) to bring the literature up to date in so far as possible, and (3) to again mention briefly the salient points regarding primary carcinoma of the Fallopian tube, some of which have been set forth in previous articles, even though this case is not entirely comparable with respect to diagnosis, since it was accidentally rather than preoperatively suspected.

According to Sanger and Barth,[1] Raynaud reported the first case of primary carcinoma of the Fallopian tube in 1847, but the first pathologic description was given by Rokitansky in 1861; Orthmann in 1886 reviewed the thirteen cases in the literature previous to that time only to exclude them as representing metastatic disease from a primary source in the uterus or ovary. Hence, he receives priority in reporting the first undoubted case of primary car-

*Presented at a meeting of the Philadelphia Obstetrical Society, Dec. 7, 1944.

†Assist. Surg. (R), U. S. Public Health Service, Resident House Physician, Lying-In Division of Pennsylvania Hospital.

‡Attending Obstetrician and Gynecologist, Chief of the Out-Patient Department, Lying-In Division of Pennsylvania Hospital.

cinoma of the tube. Many authors have contributed to a slowly growing list of case reports until to date some 449 cases have been recorded. Parsons[2] made an interesting compilation starting with Orthmann's original case in 1886. Sanger and Barth collected 17 cases in 1895. Peham found 63 cases in 1902. Doran reviewed the 100 cases reported up to 1910. Liang gathered 214 cases in 1926, and this was increased in 1929 to 230 cases by Wharton and Krock who also added 14 authentic specimens, 5 of them from Johns Hopkins Hospital and the surrounding hospitals. Nurnberger reviewed the literature again from 1886 to 1931 and was able to find 301 cases. To this number Robinson added 48 cases bringing the total to 349 up to 1935. Following this review by Parsons in 1939, Martzloff[3] reported 34 new cases "from 1935 to 1938 inclusive" bringing the total to 383. Mullins and Mosteller[4] state that Martzloff reported 392 cases up to 1938 and to this number added 35 additional cases collected from the foreign and domestic literature up to July, 1942, raising the approximate total to 427. In again reviewing the foreign and domestic literature from January, 1939, to December, 1944, we have been able to collect some 66 cases by the following authors: one case each—Cabot Case #25041,[5] P. Quinto,[6] J. N. Ficenes,[7] J. Ostrcil,[8] K. Vacha,[9] K. H. Martzloff,[3] H. A. Baron,[10] H. Wilson,[11] A. Zacho and E. Christensen,[12] T. Murasugi et al.,[13] Cabot Case #27102,[14] W. Selberg,[15] H. L. Gardner and J. C. Cain,[16] E. Hoenig and M. P. Warner,[17] D. F. Mullins and R. Mosteller,[4] D. Y. Keith,[18] and J. E. Hobbs[19]; two cases each—D. N. Henderson,[20] W. D. Fullerton,[21] J. A. Tuta and W. A. Stuhr,[22] J. O. Baker and A. Blais[23]; three cases—T. S. Kimball et al.[24]; five cases—J. L. McGoldrick et al.[25]; six cases—J. Platz,[26]; seven cases—C. Ambre[27]; eight cases—L. Parsons[2]; twelve cases—M. Berger.[28]

As Martzloff[3] and others point out, errors of tabulation creep into the literature and almost all of the reports reveal the same discrepancies. Table I shows Parsons' compilation supplemented by additional reports.

TABLE I. TABULATION OF PARSONS' COMPILATION SUPPLEMENTED BY ADDITIONAL REPORTS

AUTHOR	CASES	YEAR
Orthmann	1	1886
Sanger and Barth	17	1895
Peham	63	1902
Doran	100	1910
Liang	214	1926
Wharton and Krock	244	1929
Nurnberger	301	1886-1931
Robinson	349	1936
Martzloff	383	1940
Mullins and Mosteller	427	1943
Authors'	449	1944

Incidence

The incidence in various hospital centers is roughly similar. Wharton and Krock[29] report five cases among 35,000 gynecologic patients at Johns Hopkins Hospital. Gupta[30] in Calcutta found one specimen among 6,000 patients with pelvic disease. Barrows[31] noted three cases among 30,000 patients on the gynecologic wards at the Bellevue Hospital in New York City. Holland[32] reported nine cases in 10,000 complete salpingectomies done at the Mayo Clinic. Anspach[33] found one case in 19,439 patients on the gynecologic service at the University Hospital in Philadelphia. Fullerton estimates one primary carcinoma in every 1,000 salpingectomies from his studies made in Cleveland. Hoffman and Anspach[34] report the condition once in 4,275 cases admitted to the gynecologic service of the Jefferson Hospital in Philadelphia over a period of nine years. We have been able to verify but this one case in 6,149 surgical speciments of Fallopian tubes taken for microscopic examination at the Pennsylvania Hospital since the founding of the Ayer Clinical Laboratory in 1898. The frequency of primary carcinoma of the tube among tumors of the genital tract is found to vary in the literature from 0.03 per cent to 1.35 per cent and is considered to average about 0.5 per cent. Johnson and Miller[35] report a case in a girl 18 years of age and Fullerton[21] a case in an 80-year- old woman. Age apparently has little or no influence on the disease. However, the greatest incidence occurs in the fifth decade. Unilateral involvement occurs in 70 per cent of the cases and bilateral lesions occur in 30 per cent of the cases. Secondary carcinoma of the Fallopian tube is ten times as frequent as primary carcinoma. These data are shown in Table II.

TABLE II. INCIDENCE OF PRIMARY CARCINOMA OF FALLOPIAN TUBE FOUND IN VARIOUS HOSPITAL CENTERS

Wharton and Krock	5 cases in 35,000 gyn. patients
Gupta	1 specimen in 6,000 patients
Barrows	3 cases in 30,000 gyn. patients
Holland	9 cases in 10,000 salpingectomies
Anspach	1 case in 19,439 gyn. patients
Hoffman and Anspach	1 case in 4,275 gyn. patients
Fullerton	1 case in 1,000 salpingectomies
Authors'	1 case in 6,149 salpingectomies

Frequency among genital tumors—0.5%
Age: youngest, 18 yr.; oldest, 80 yr.; greatest incidence in fifth decade
70%, unilateral; 30%, bilateral; distal two-thirds, common site

Etiology

Although the etiological factor in primary carcinoma of the Fallopian tube is unknown, Sanger and Barth,[1] Ewing,[36] and others believe inflammatory pelvic disease predisposes, but Peham,[37] Wechsler,[38] Liang,[39] Vest,[40] Gupta,[30] and others do not agree with this hypothesis. Fullerton[21] states that the frequency of coincident tuberculosis may be of importance in stimulating formation of benign papillomas which later become malignant.

Pathology

The most frequent site of predilection is the distal two-thirds of the organ. Robinson,[41] in his article quoting Nurnberger, states that the diagnosis of primary carcinoma of the Fallopian tube depends on proving the original source to be endosalpinx. If the anatomic landmarks are still present, this is not difficult. Primary carcinoma involves the mucosa first before extending to the muscularis, while secondary carcinoma usually forms deposits on or in the wall of the tube before it affects the mucosa. According to Robinson,[41] Friedenheim and others described three types of tubal carcinoma: the papillary, the adenomatous, and the alveolar. The earliest variety is the papillary, the latest variety is the alveolar, and the adenomatous apparently is an intervening or intermediary phase. Two or more phases may be demonstrable in the same tube. McGoldrick et al.[25] state there are two kinds: the papillary and the infiltrative. The papillary variety grows into the lumen of the tube and the infiltrative variety grows into the wall of the tube. Grossly, the tubes may vary in appearance from the normal salpinx to a greatly distorted, distended, blunt-ending structure. Microscopically, benign tumors generally show but a single layer of epithelial cells covering the folds or lining the pseudoadenomatous spaces formed by adherent folds. These epithelial cells and their nuclei are uniform in size, shape, and staining quality. Malignant growths generally show several layers of epithelial cells which are irregular in size and shape. The irregularity in the staining quality of their large nuclei, which show numerous mitotic figures, is commonplace. Invasion of the tubal wall is usually a late occurrence or may be entirely absent. Tubal epithelium is normal except where involved. It is necessary sometimes to differentiate primary carcinoma of the Fallopian tube from endometrioma, tuberculosis, and chronic inflammation of the tube wall. Willis[42] states that metastases have been found in the cervix and fundus uteri, ovary, vagina, bladder, kidney, liver, lungs, stomach, large intestines, diaphragm, spleen, skin, and supraclavicular nodes long before the tubal wall has been involved. According to the information based on clinical and pathologic observations made by Cullen,[43] Liang,[39] Vest,[40] and others, the lymphatic route is considered to be the only route of dissemination. McGoldrick et al.,[25] state that the pathways are those along the upper margin of the broad and infundibulopelvic ligaments and ovarian vessels to the iliac, aortic, and lumbar nodes. Metastases have been known to spread via lymphatics of the round ligaments and produce enlarged inguinal lymph nodes. Other methods for development of metastatic lesions by way of continuity, contiguity, transperitoneal migration, and vascular channels must not be overlooked.

Symptoms

Parsons[2] states: "Bleeding is the earliest and most important single symptom"; and "Pain appears early in the disease in contrast to cancer of fundus or ovary." The symptom complex of intermittent colicky pain associated with a constant, intermittent, or sudden gush of water, yellow or bloody fluid from the vagina, followed by relief of pain, is

suggestive of carcinoma of the Fallopian tube. Robinson[41] states that Latzko, in 1915, first noted this symptom complex calling it "hydrops tubae profluens," and, in 1922, Stanca described this symptom complex in detail. Fullerton[21] says there are no distinctive symptoms. There may be disturbance of menstrual function with some increase in frequency and irregularity. Postmenopausal bleeding may develop. Hydrops tubae profluens, when present, is suggestive, and if the odor of the discharge is foul, necrosis is present.

Diagnosis

Preoperative diagnosis of primary carcinoma of the Fallopian tube is difficult as reflected by the paucity of such cases in the literature. Parsons[2] considers the most important single fact in the diagnosis "the necessity for suspecting the probable existence of a tubal carcinoma where bleeding has recurred after a negative curettage in an atrophic uterus." Hobbs[19] states that every gynecologist knows that when a woman has a serous or serosanguineous discharge from the cervix, three lesions are to be considered: (1) uterine carcinoma, (2) hydrops tubae profluens, and (3) primary carcinoma of the Fallopian tube.

Treatment

The usual accepted form of treatment is a total hysterectomy and a bilateral salpingo-oophorectomy. Some cases are also given postoperative irradiation with high voltage roentgen therapy. Even so the results are poor. Martzloff,[3] in studying cases where postoperative roentgen therapy had been used, concluded that there was an "absence of factual support for such a recommendation." Hobbs[19] suggests leaving the cervix and a portion of the corpus uteri in situ, the cervical and uterine canal acting as a receptacle for later radium insertions. Radium can thus be used in combination with deep roentgen therapy. Clinically, the importance of the fact that 30 per cent of the reported cases are bilateral must not be overlooked. An apparently normal-appearing opposite tube should not prevent a radical procedure.

Prognosis

Parsons[2] states that "the most important element in consideration of carcinoma of the tube lies not in its rarity but in the fact that it represents the most malignant form not only in genital carcinoma but of carcinoma anywhere in the body." To further emphasize this statement, he mentions his findings of a survival rate less than 4 per cent of three-year cures without roentgen therapy. Fullerton[21] says that not more than 5 per cent get a five-year cure.

Report of Case

M. B., No. 27,353, a 23-year-old white woman, first registered in the Out-Patient Department of the Lying-In Division of the Pennsylvania Hospital, June 6, 1940. Her prenatal course was entirely uneventful and she was delivered by low forceps and episiotomy, March 4, 1941, of a normal full-term female infant. The postpartum course was normal and the patient was discharged on her tenth postdelivery day. She again registered in the prenatal clinic, May 13, 1942, two months pregnant. This pregnancy was of necessity interrupted on Oct. 1, 1942, by an emergency classical cesarean section for central placenta praevia. The mother's postoperative course was uneventful except for three days' morbidity. She was discharged twelve days postoperative in good condition. This patient was next seen on July 28, 1943, when again she registered in the prenatal clinic two months pregnant. She was classified "abnormal" since she had had a previous caesarean section. The interval history was negative. Her prenatal course proved entirely satisfactory and the patient entered the ward for an elective caesarean section and sterilization. The laboratory examinations were negative. One Feb. 25, 1944, under continuous caudal analgesia, a normal full-term male infant was delivered by a Kerr cesarean section, and Pomeroy's modified Madlener's sterilization operation was performed. The postoperative course was smooth. An excerpt from the description of the operative procedure is as follows: "Both tubes were grasped in their middle thirds and a ligature of No. 3 chromic catgut was tied around each loop. The loops were resected." The specimens of the resected segments of Fallopian tubes were sent to the laboratory for routine confirmation. Gross examination (S. No. 37,636) was as follows: "Specimen in formalin consists of two small pieces

of tissue resembling segments of Fallopian tube. They measure 20 mm. × 5 mm., and 13 mm. × 5 mm., respectively. The external surfaces are smooth, glistening, and except for areas of trauma sustained at the time of removal, are not remarkable in appearance. Cross section of the specimens reveals no unusual appearance in the region of the lumina. Sections taken for microscopic study are from the mid- portions of the specimens.'' Microscopic examination by Dr. John T. Bauer, Director of the Ayer Clinical Laboratory was as follows:

Microscopic Examination.—''The size and contour of the uterine tubes on section are normal. The surface mesothelium is regular, flat and intact. The subserosal tissue and tubo-ovarian ligament are edematous, containing well separated, swollen strands of narrow smooth muscle fibers and a number of dilated but empty arteries, veins and capillaries. A sparse scattering of lymphocytes, occasional monocyte, fibroblast and a rare plasma cell

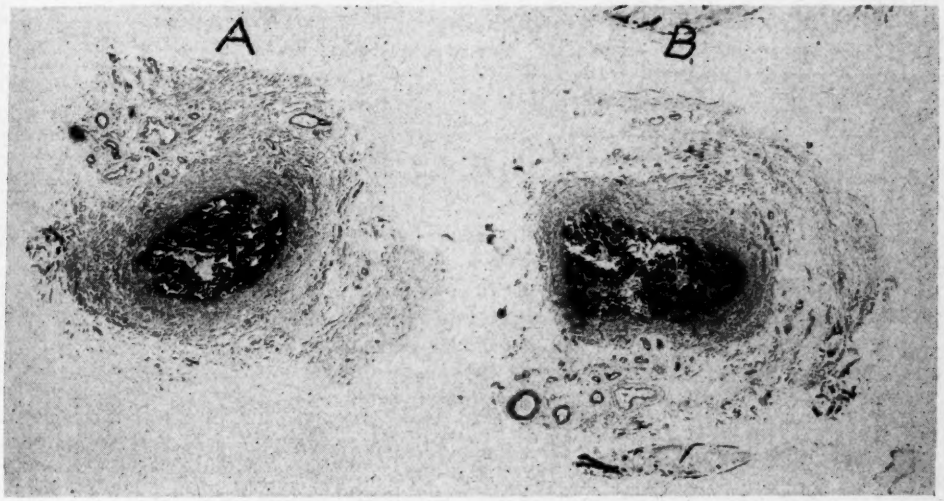

Fig. 1.—Topographical photomicrograph showing sections of normal Fallopian tube (*A*) and abnormal Fallopian tube (*B*). (×9.)

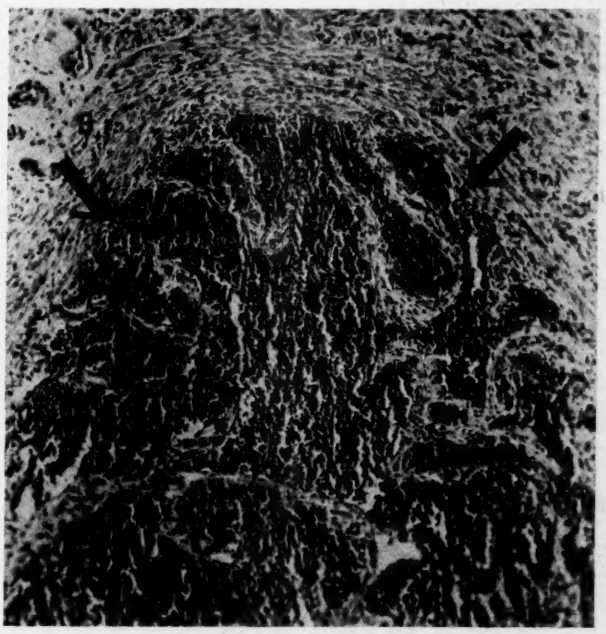

Fig. 2.—Low-power photomicrograph showing region of tumor illustrating sharp line of demarcation between muscularis and endosalpinx. Compare with area shown in Fig. 5. Arrows, *A* and *B*, indicate locations shown in Fig. 3 and 4, respectively. (×130.)

exists in the tissue about these vessels. There is a little swelling of the walls of the small veins and arterioles, but the endothelium is not swollen. However, in the deeper subserosa where the underlying muscle fibers become more abundant to form the muscular coat of the uterine tube, lumina of several small vessels become filled but not distended with small pale oval cells containing sparse cytoplasm surrounding pale vesicular nuclei which deviate somewhat at times from an oval shape. The muscle fibers are somewhat pale, swollen, and a little edema exists between them. A few of the small vessels can be traced on serial sections from the subserosa through the muscular coat, pursuing a tortuous course to the submucosa.

"In the lumina of some of these vessels, cells such as those just described seem to be making their passage from the mucosa. The cellular infiltration noted in the subserosa is a trifle more noticeable in the muscular coat and is occasionally accompanied by a polymorphonuclear neutrophile. Thus far all of the changes with the exception of the cells within the lumina of vessels are those customarily observed in a recent intra-uterine pregnancy. From here on, however, the pregnancy changes are overshadowed by those of a low grade malignant, almost benign epithelial neoplasm. The innermost portion of the muscular coat is not clearly demarcated from the submucous and mucosal folds of the tube. Strands of fibrous tissue extend into the lumen, and sheets of the epithelial cells appear to separate some of the muscle bundles and fibers. Capillaries and other small vessels such as those described in the subserosa, penetrate to within a few cells of the solid columns and sheets of proliferative epithelium which replaces most of the normal columnar epithelium that lines the uterine tube. No well defined lumen exists. Instead the columnar epithelium which in places is regular and forms small tubular structures merges with solid masses of epithelial cells that are separated by thin vascularized strands of fibrous tissue which tend neither to form alveoli or papillary stalks. The neoplastic epithelial cells which indistinctly merge with remaining normal columnar epithelium are small with scant, slightly basophilic cytoplasm and surrounding relatively large oval or circular nuclei possessing an increased amount of reticular and granular chromatin which makes them stain a trifle more intensely than the nuclei of normal cells. On the whole these cells are fairly regular. The nuclei vary little in shape and size. Dividing cells are not numerous. There is no reticulum between these solid nests of compact neoplastic cells.

"Throughout the series of sections the solid structures of the neoplastic islands gradually give way to compressed tubular structures and then to the normal arrangement of regular columnar epithelium from which the solid nests have apparently originated. The tumor, despite its local invasiveness and spread through some of the deeper vascular channels to the subserosa, appears relatively benign. Masson's trichrome stain, Masson's silver stain, Mallory's phosphotungstic acid hematoxylin and his modification of Heidenhain's azan-carmine stain confirm the appearance of the hematoxylin-eosin stained preparations."

Pathologic Diagnosis.—"Segments of Fallopian tubes: one segment appears normal, the other segment shows primary carcinoma and both segments show pregnancy changes consisting of swollen smooth muscle fibers."

In view of these findings it was deemed advisable to subject this patient to a total hysterectomy and bilateral salpingo-oophorectomy. This operation was performed three weeks from the day of the Kerr cesarean section. An excerpt from the description of the operation follows: "The uterus was found to be fairly well involuted and healed from the previous operation. Each tube was adherent to the parietal peritoneum at the border of the pelvis and in the right tube there appeared to be some thickening. These adhesions of the tube were at the site of ligation." Doctor Bauer's study of these specimens revealed no further evidence of neoplastic change in the uterus, ovaries, and regions proximal and distal to the points of ligation and resection of the Fallopian tubes. The patient's postoperative course was normal and discharge was granted her thirteen days later, March 30, 1944. The entire hospital stay amounted to thirty-four days. She was again seen in the Special Follow-Up Tumor Clinic May 9, 1944. The note follows: "Weight 110 pounds. The patient feels fine, looks fine, is fine. Pelvis negative. Return in six months." On Nov. 14, 1944, the patient made her second visit to the Tumor Clinic. The physical examination was entirely negative. She had gained 6 pounds in weight and felt fine. Deep roentgen therapy has been instituted.

Discussion

Interesting features of this case are these: (1) the accidental manner in which the tumor was discovered, (2) the occurrence of primary carcinoma of

the Fallopian tube with a normal intrauterine gestation at term, (3) the histopathologic study, and (4) the importance of a routine pathologic examination of tissues.

The small segment of tissue which contained the abnormality was located in the distal two-thirds of the Fallopian tube. This is the area of predilection for carcinoma of the Fallopian tubes. It just happened that this particular region, usually the middle third of the tube, was selected for resection at the time of the Pomeroy modification of Madlener's sterilization operation. Microscopically, this section of tissue proved to contain a primary neoplasm. Which tube was involved remains a mystery.

Fig. 3.

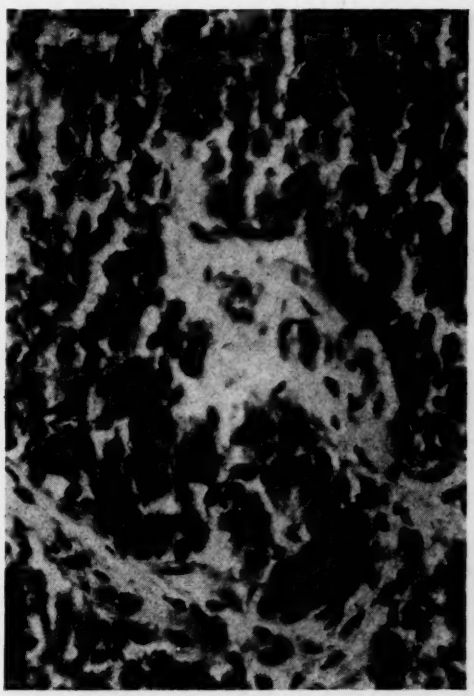

Fig. 4.

Fig. 3.—High-power photomicrograph showing cords of neoplastic cells and a pseudoadenomatous area. Arrow *A*, Fig. 2. (×580.)

Fig. 4.—High-power photomicrograph showing several layers of epithelial cells lining pseudoadenoma, normal columnar tubal epithelium, and cords of neoplastic cells. Arrow *B*, Fig. 2. (×580.)

The association of carcinoma of the Fallopian tube with a full-term intrauterine pregnancy is purely coincidental and perhaps of little significance. The only demonstrable pregnancy change in the sections of the Fallopian tube is the swollen smooth muscle fibers. No decidual elements could be detected. Whether or not this region of the tube previously contained a benign papilloma whose growth might have been stimulated by effects of gestation remains conjectural.

The histopathologic study shows that the neoplasm is young enough that the merging of normal columnar epithelium of the endosalpinx with the solid masses of neoplastic cells can be demonstrated (Figs. 3 and 4). The criterion needed for the diagnosis of a primary neoplasm of the Fallopian tube as pointed out by Robinson,[41] quoting Nurnberger, is thus fulfilled. The microscopic description

Fig. 5.—Low-power photomicrograph showing cord formations of neoplastic cells and the tendency for cords to invade tubal wall. Lymph and vascular channel invasion shown. Arrows *A* and *B*, indicate locations shown in Figs. 6 and 7, respectively. Pregnancy change consists of swollen smooth muscle fibers. (×130.)

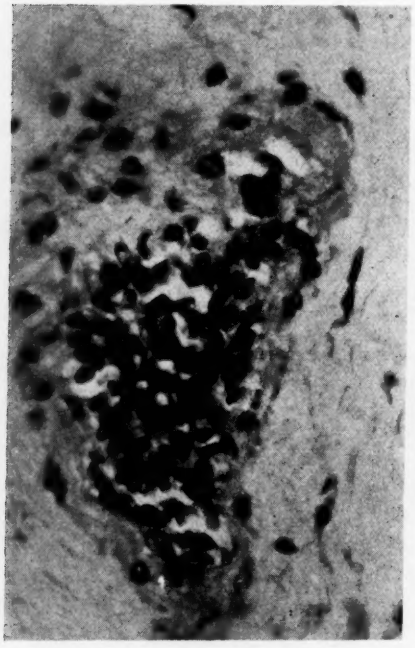

Fig. 6.

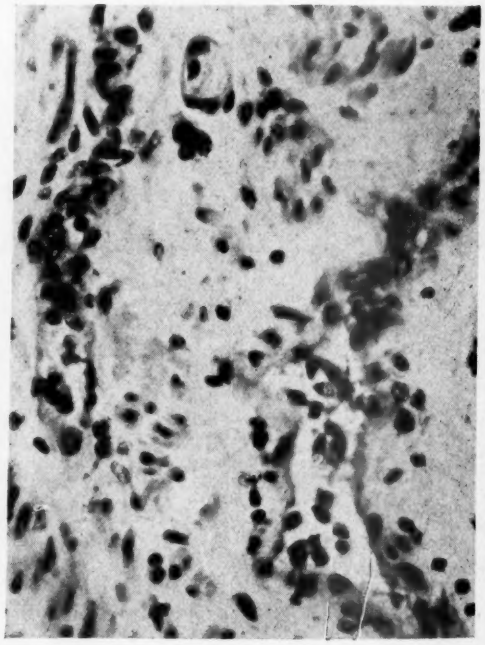

Fig. 7.

Fig. 6.—High-power photomicrograph showing vascular channel invasion by neoplastic cells. Arrow *A*, Fig. 5. (×580.)

Fig. 7.—High-power photomicrograph showing lymph channel invasion by neoplastic cells. Arrow *B*, Fig. 5. (×580.)

of this specimen fits both Freidenheim's classification and McGoldrick's grouping. This tumor gives the impression of growing toward the lumen of the tube which is the characteristic of the papillary variety. This diagnosis was confirmed by Novak.[44] Also, in one region of the microscopic section, the continuity of the line of demarcation between muscularis and endosalpinx appears to be broken, suggesting a tendency toward infiltration of the tube wall (Fig. 5). Thus, both varieties of primary carcinoma of the Fallopian tube may be manifest in the same specimen. The adherence of the folds produces the pseudoadenomatous appearance shown in Figs. 2, 3, 4, and 5. Lymph channels and vascular channels filled with neoplastic cells in the process of migration even at this apparently early stage of carcinomatous growth can be demonstrated (Figs. 6 and 7). The neoplastic cells are described as "small and regular." The cells have a scant basophilic cytoplasm surrounding large oval or circular nuclei which stain more intensely than normal cell nuclei. Few mitotic figures are noted and the nuclei vary little in size and shape. This leads to the idea that this tumor is relatively benign. However, the fact that invasion of the tube wall is suggestive, that neoplastic cells are demonstrable in lymph and vascular channels, that cord formations (carcinoma simplex) of neoplastic cells are prominent, and that there are areas showing several layers of epithelial cells covering the folds or lining the pseudoadenomatous spaces—all direct attention to the fact this lesion may not be as benign or of as low a grade of malignancy as was first suspected. Dr. Bauer's subsequent report on the microscopic appearance of the Fallopian tubes removed at the time of the total hysterectomy and bilateral salpingo-oophorectomy revealed the lesion apparently had been removed in its entirety when the operation for sterilization was done. Perhaps that procedure alone would have accidentally resulted in a cure; but, in the light of the unfavorable prognosis given to this disease, the complete extirpation of the uterus, tubes, and ovaries was considered imperative.

Had the segments of Fallopian tube been examined grossly at the operating table, the lumen identified, and the specimen discarded (rather than sent to the laboratory for routine microscopic confirmation of structure) the new growth probably would not have been discovered until clinically it had reached a much further advanced stage.

References

1. Sanger, M., and Barth, J.: Die Neubildungen der Eileiter: In Martin, A.: Die Krankenheiten der Eileiter, Leipzig, 1895, Eduard Besold.
2. Parsons, L.: New England J. Med. **221**: 367, 1939.
3. Martzloff, K. H.: Am. J. Obst. & Gynec. **40**: 804, 1940.
4. Mullins, D. F., and Mosteller, R.: Am. J. Obst. & Gynec. **45**: 1042, 1943.
5. Cabot Case No. 25041, New England J. Med. **220**: 161, 1939.
6. Quinto, P.: Riv. ital. di gynec. **22**: 3, 1939.
7. Ficenes, J. N.: Ginek. polska **18**: 65, 1939.
8. Ostreil, J.: Ceskoslov. gynaek. **18**: 25, 1939.
9. Vacha, K.: Ceskoslov. gynaek. **18**: 205, 1939.
10. Baron, H. A.: Canad. M. A. J. **43**: 118, 1940.
11. Wilson, H.: Roy. Melbourne Hosp. Clin. Rep. **11**: 44, 1940.
12. Zacho, A., and Christensen, E.: Acta obst. et gynec. Scandinav. **21**: 63, 1941.
13. Murasugi, T., Kawasina, T., and Nakai, K.: Jap. J. Obst. and Gynec. **24**: 43, 1941.
14. Cabot Case No. 27102: New England J. Med. **224**: 427-428, March 6, 1941.
15. Selberg, W.: Dermat. Wehnschr. **113**: 579, 1941.
16. Gardner, H. L., and Cain, J. C.: Am. J. Obst. & Gynec. **42**: 522, 1941.
17. Hoenig, E., and Warner, M. P.: M. Rec. **155**: 271, 1942.
18. Keith, D. Y.: Kentucky M. J. **41**: 74, 1943.
19. Hobbs, J. E.: South. M. J. **35**: 733, 1942.
20. Henderson, D. N.: Am. J. Obst. & Gynec. **37**: 321, 1939.
21. Fullerton, W. D.: Am. J. Surg. **48**: 467, 1940.
22. Tuta, J. A., and Stuhr, W. A.: Am. J. Clin. Path. **11**: 864, 1941.
23. Baker, J. O., and Blais, A.: Canad. M. A. J. **46**: 67, 1942.

24. Kimball, T. S., Sanford, H. E. and Brown, A. F.: California & West. Med. **57**: 351, 1942.
25. McGoldrick, J. L., Strauss, H., and Rao, J.: Am. J. Surg. **59**: 555, 1943.
26. Platz, J.: Arch. f. Gynäk. **170**: 604, 1940.
27. Ambre, C.: Gynécologie **38**: 89, 1939.
28. Berger, M.: Lijecn. vjes. **63**: 93, 1941.
29. Wharton, L. H., and Krock, F. H.: Arch. Surg. **19**: 848, 1929.
30. Gupta, N.: J. Obst. & Gynaec. Brit. Emp. **38**: 839, 1931.
31. Barrows, D. N.: AM. J. OBST. & GYNEC. **13**: 710, 1927.
32. Holland, W. W.: Surg. Gynec. & Obst. **51**: 683, 1930.
33. Anspach, B. M.: AM. J. OBST. & GYNEC. **20**: 571, 1930.
34. Hoffman, J., and Anspach, B. M.: AM. J. OBST. & GYNEC. **22**: 424, 1931.
35. Johnson, W. O., and Miller, A. J.: Ann. Surg. **93**: 1208, 1931.
36. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 3, Philadelphia and London, 1928, W. B. Saunders Co., p. 653.
37. Peham: Ztschr. f. Heilk. **24**: 317, 1903.
38. Wechsler, H. T.: Arch. Path. **2**: 161, 1926.
39. Liang, Z.: Arch. f. Path. Anat. **259**: 577, 1926.
40. Vest, C. W.: Bull. Johns Hopkins Hosp. **25**: 305, 1914.
41. Robinson, M. R.: AM. J. OBST. & GYNEC. **32**: 84, 1936.
42. Willis, R. A.: The Spread of Tumors in the Human Body, London, 1934, J. and A. Churchill, p. 283.
43. Cullen, T. S.: Bull. Johns Hopkins Hosp. **22**: 20, 1911.
44. Novak, E.: Personal communication.

AQUINONE* DURING LABOR; ITS EFFECT ON THE PROTHROMBIN LEVEL OF THE NEWBORN INFANT†

HERBERT E. SCHMITZ, M.D., AND GEORGE BABA, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Loyola University School of Medicine, and the Lewis Memorial Maternity Hospital)

A STUDY of prothrombin levels in the newborn infant requires the consideration of many factors. Recent literature reports the prothrombinopenic effects of drugs, such as certain barbiturates[4, 5, 17] and salicylates,[15] as well as the beneficial effect on newborn infants, of Vitamin K administration to laboring mothers. Furthermore, the institution of early extra feeding schedule has been shown to have a prophylactic effect against the development of prothrombinemia in the newborn.[13, 14] Thus, determinations of the prothrombin level in newborn infants lose their significance unless correlated with maternal conditions prior to parturition and with feeding schedules.

Errors in technique should be reduced to the minimum by the adoption of certain standards. The elements of human error can be ignored when the same personnel handles all the procedure. The effect of temperature must be eliminated by allowing enough time for the reagents to reach room temperature. This is important, since the prothrombin clotting time will be materially prolonged by the use of reagents below the prevailing room temperature.[8] The ideal in controls is reached by the use of two or three newborn infants past the sixth postnatal day and with normal clotting time (100 per cent) for at least the last two days.

Procedure

Freshly extracted Bacto-thromboplastin[2] was used in the dilution wherein the clotting time of normal blood falls in the range of 25 to 30 seconds. Thirty to forty cubic millimeters

*Aquinone supplied by a grant from Ernst Bischoff Co., Inc., Ivoryton, Conn.
†Presented before a regular meeting of the Chicago Gynecological Society, Nov. 17, 1944.

of the free-flowing blood from a lanced heel was immediately mixed on a clean slide with 10 c.mm. of the reagent. The clotting time was determined by tilting the glass back and forth until the clot formed.

$$\text{Clotting time in per cent} = \frac{\text{Clotting time of normal}}{\text{Clotting time of patient}} \times 100.$$

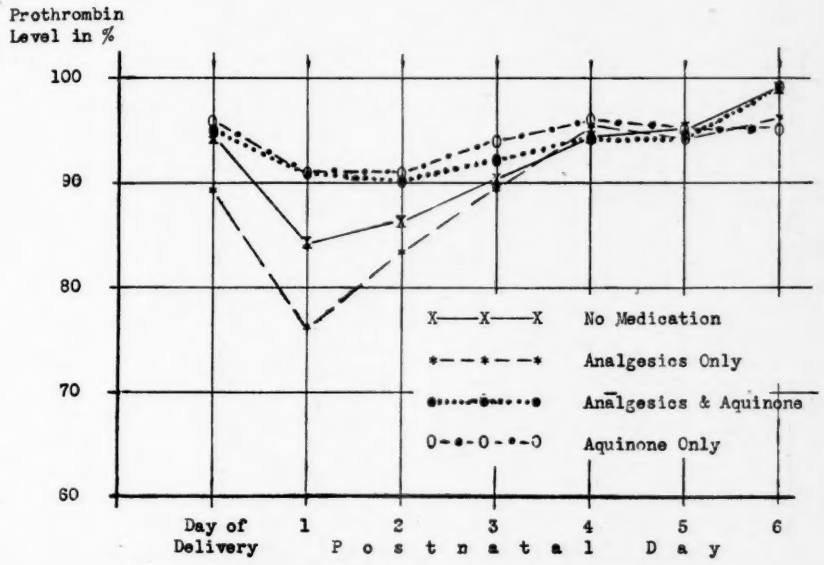

Fig. 1.—Average prothrombin level of the newborn infants.

TABLE I. TOTAL NUMBER OF CASES DETERMINED, TOTAL PERCENTAGE (PROTHROMBIN LEVEL), AND AVERAGE LEVEL

	NO MEDICATION		ANALGESICS ONLY		ANALGESICS AND AQUINONE		AQUINONE ONLY	
Day of delivery								
No. of cases	137		43		63		23	
Total per cent	12902		3821		6011		2216	
Average per cent		94		89		95		96
Postnatal 1								
No. of cases	166		53		74		27	
Total per cent	13930		4055		6775		2457	
Average per cent		84		76		91		91
Postnatal 2								
No. of cases	163		52		75		28	
Total per cent	14148		4310		6796		2548	
Average per cent		86		83		90		91
Postnatal 3								
No. of cases	153		51		74		28	
Total per cent	13828		4541		6857		2642	
Average per cent		90		89		92		94
Postnatal 4								
No. of cases	149		48		67		27	
Total per cent	14116		4500		6354		2601	
Average per cent		94		95		94		96
Postnatal 5								
No. of cases	140		49		66		27	
Total per cent	13320		4621		6238		2583	
Average per cent		95		94		94		95
Postnatal 6								
No. of cases	138		48		63		23	
Total per cent	13711		4650		6265		2185	
Average per cent		99		96		99		95

TABLE II. THE DAY OF MINIMUM PROTHROMBIN LEVEL

	NO MEDICATION		ANALGESICS ONLY		ANALGESICS AND AQUINONE		AQUINONE ONLY	
TOTAL NO. OF CASES	165		56		80		30	
No drop								
No. of cases	16		0		13		7	
Per cent of cases		10		0		16		23
Day of delivery								
No. of cases	14		7		12		3	
Per cent of cases		8		12.5		15		10
Postpartum 1								
No. of cases	61		33		17		7	
Per cent of cases		37		59		21		23
Postpartum 2								
No. of cases	44		13		17		9	
Per cent of cases		27		23		21		30
Postpartum 3								
No. of cases	22		2		13		1	
Per cent of cases		13		4		16		3
Postpartum 4								
No. of cases	7		0		6		3	
Per cent of cases		4		0		7.5		10
Postpartum 5								
No. of cases	1		1		2		0	
Per cent of cases		1		2		2.5		0

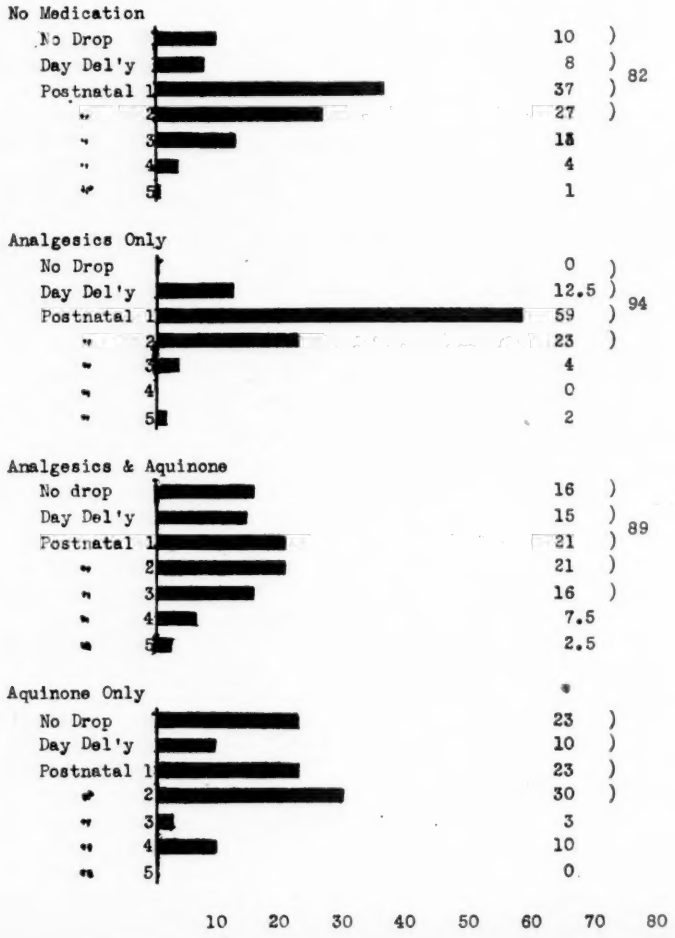

Fig. 2.—The day of minimum prothrombin level (in per cent).

This study was conducted by the same two residents. Reagents were not used until they were of room temperature. Separate controls were used in the different nurseries, since the temperatures varied in each. The average of two or three infants past the sixth postnatal day, having 100 per cent clotting time for at least the two preceding days, was used for control.

Analysis of Data

A total of 231 unselected cases of newborn infants was investigated. They were classified according to whether the laboring mother had received no medication, some form of analgesia (usually cyclopal sodium), both analgesia and aquinone, or only aquinone. The amount of analgesics given differed with the duration of labor, but only one ampule of aquinone was given intramuscularly in a twenty-four-hour period. Prothrombin levels were made on the day of delivery and for six days thereafter.

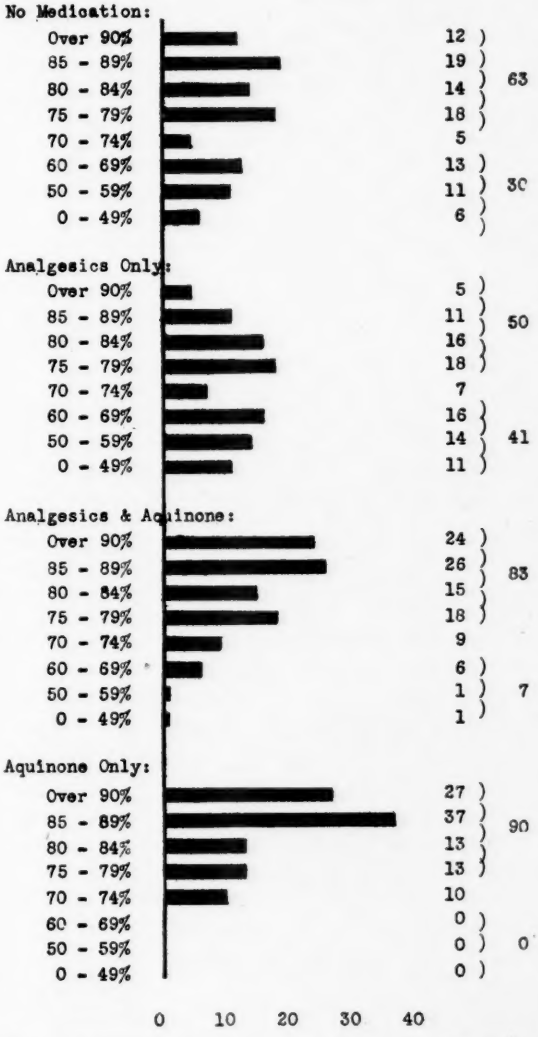

Fig. 3.—Prothrombin level on the first day of minimum level.

The data were analyzed to determine the minimum level and the day by which this level was reached. When the average levels are plotted (Table I), a precipitous drop by the first day is shown for the groups where no aquinone was used (Fig. 1), while the groups with aquinone showed but a slight drop.

Further analysis, however, will correct the misleading implications of generalizations as in Fig. 1 (See Tables II and III, and Figs. 2 and 3). The classification of "no drop" is used to designate those cases in which the minimum level never fell below the 92 per

TABLE III. PROTHROMBIN LEVEL ON THE FIRST DAY OF MINIMUM LEVEL

	NO MEDICATION		ANALGESICS ONLY		ANALGESICS AND AQUINONE		AQUINONE ONLY	
TOTAL NO. OF CASES	165		56		80		30	
Over 90 per cent								
No. of cases	20		3		19		8	
Per cent of cases		12		5		24		27
85-89 per cent								
No. of cases	32		6		21		11	
Per cent of cases		19		11		26		37
80-84 per cent								
No. of cases	24		9		12		4	
Per cent of cases		14		16		15		13
75-79 per cent								
No. of cases	30		10		14		4	
Per cent of cases		18		18		18		13
70-74 per cent								
No. of cases	9		4		7		3	
Per cent of cases		5		7		9		10
60-69 per cent								
No. of cases	22		10		5		0	
Per cent of cases		13		16		6		0
50-59 per cent								
No. of cases	12		8		1		0	
Per cent of cases		11		14		1		0
0-49 per cent								
No. of cases	10		6		1		0	
Per cent of cases		6		11		1		0

cent level. This is because 8 per cent represents only 2 seconds difference in the clotting time (see *Procedure*) and is within the margin of error. Others represent the first day of minimum level. When two or more successive days differed by only 2 per cent, the first day on which the low level occurred was regarded as the first day of minimum level:

Day of delivery	Postnatal i	ii	iii	iv	v	vi
--	--	--	82	80	84	

The postnatal iii day was taken. Again, the 2 per cent represents ½ second difference in the clotting time and is therefore not measurable.

As can be seen from Fig. 2, the day of minimum level is not as clear cut as one is led to believe when only the averages are considered (Fig. 1).

With no medication, 82 per cent were at the minimum level by the second full postnatal day, but 64 per cent dropped to the minimum level on the first and second day. When analgesics were used, 94 per cent dropped to the minimum level by the third day, but 59 per cent were at the minimum level on the first postnatal day. When analgesics and aquinone were both used, 89 per cent fell to the minimum level by the third day but the fall was spread fairly evenly over the four days. When aquinone alone was used, 86 per cent fell to the minimum level by the third postnatal day, with the greatest number (30 per cent) occurring on the second postnatal day.

A study of the actual amount of fall to the minimum level is interesting (Fig. 3). The percentage of cases remaining above the 75 per cent minimum level is as follows: no medication, 63 per cent; analgesics alone, 50 per cent; both analgesics and aquinone, 83 per cent; aquinone alone, 90 per cent. More significant than the above is the percentage of cases falling below the 70 per cent level, since many clinicians consider values below this level to be an indication for vitamin K therapy (in diseases accompanied by prothrombinemia), and values below 40 as definitely in the danger zone. Where no aquinone was used, the percentages were 30 per cent and 41 per cent for the "no medication" group and the "analgesics only" group, respectively, while where the aquinone was used, the percentage was 8 and 0 for the "aquinone-analgesic" group and the "aquinone alone" group, respectively.

Miscellaneous Finding

In this small series no definite conclusion can be drawn, but, nevertheless, certain incidental observations are set forth. Icterus of varying degree was frequently seen in spite of the high or normal prothrombin level (over 92 per cent). In some, the icterus was quite marked in spite of the normal clotting time. On the other hand, other cases with prothrombin level below 40 per cent manifested no icterus.

Discussion

A review of the literature brings out conflicting views regarding the value of vitamin K in obstetrics. Parks and Sweet[12] conclude that it has no evident effect in reducing the incidence of neonatal hemorrhage. Hellman and his associates,[7] on the other hand, contend that the incidence of hemorrhage in the non-vitamin K group is too striking to be mere coincidence. Maumenee and associates[11] report a greater incidence of retinal hemorrhage in the non-vitamin K group than in the vitamin K group.

For a proper evaluation of any antihemorrhagic factor, it is important that all variables be considered. Thus, according to Howell's theory of the clotting of blood, prolonged bleeding may result from deficiencies of fibrinogen, calcium, thromboplastin, platelets, and prothrombin, as well as to an excess of the antithrombin factor (heparin). Even when all the component factors are quantitatively normal, bleeding may still be prolonged as in the case of a hemophiliac. Then, too, must be considered such factors as the degree and the extent of trauma initiating bleeding.

The role of hypoprothrombin in the hemorrhagic disease of the newborn may best be summarized by quoting Eastman: "Hypoprothrombinemia introduces . . . a new concept of hemorrhagic diathesis in the newborn. Far from being a disease entity unto itself, it represents, simply, an extreme degree of a condition hypoprothrombinemia, which all newborn infants exhibit to a certain extent and in various gradations. Unless the plasma prothrombin level is extremely low, the hypoprothrombinemia may be without clinical manifestation. However, if birth trauma, anoxia, and other causes of bleeding are superimposed upon it, the prothrombin lack must necessarily play a part in the duration and, therefore, the extent of bleeding. . . ."

Theoretically, circumstances tending to produce fetal hemorrhage may be present as soon as labor begins. Should intrauterine prothrombinemia exist because of inadequate vitamin K synthesis or intake, and permit the operation of such factors as mechanical pressure, transient relative anoxia, etc., fetal hemorrhage might occur at any time during labor. Hence, it follows that the vitamin K administration should be sufficiently early to eliminate the role of prothrombinemia in the production of hemorrhage.

Conclusions

1. There is a physiologic hypoprothrombin state reaching the minimum level in most cases by the third postnatal day.

2. Labor analgesics in the form of certain barbiturates apparently exert prothrombinopenic effect on the newborn infants.

3. Aquinone to laboring mothers has a prophylactic effect against physiologic or induced prothrombinemia.

4. Icterus of the newborn infant may not be associated with hypoprothrombin state.

5. Aquinone intramuscularly caused no discomforting symptoms.

References

1. Butt, H. R., and Snell, A. M.: Vitamin K, Philadelphia, 1941, W. B. Saunders Co.
2. Difco, Laboratories: Directions for preparing Bacto-Thromboplastin Extract.
3. Eddy, W. H., and Dalldorf, G.: The Avitaminosis, Baltimore, 1941, Williams & Wilkins Co., pp. 427-440.
4. Fitzgerald, J. E., and Webster, A.: J. A. M. A. **119**: 1082, 1942.
5. Fitzgerald, J. E., and Webster, A.: Am. J. Obst. & Gynec. **40**: 413, 1940.
6. Hellman, L. M., Moore, W. T., and Shettles, L. B.: Bull. Johns Hopkins Hosp. **66**: 379, 1940.
7. Hellman, L. M., Shettles, L. B., and Eastman, N. J.: Am. J. Obst. & Gynec. **40**: 844, 1940.
8. Kato, K., and Poncher, H. G.: J. A. M. A. **114**: 749, 1940.
9. Kato, Katsuji: Clinics **2**: 33, 1943.
10. Kracke, Roy A.: Diseases of the Blood, ed. 2, Philadelphia, 1941, J. B. Lippincott Co., pp. 633-644.
11. Maumenee, A. E., Hellman, L. M., and Shettles, L. B.: Bull. Johns Hopkins Hosp. **68**: 158, 1941.
12. Parks, J., and Sweet, L. K.: Am. J. Obst. & Gynec. **44**: 432, 1942.
13. Pray, L. G.: Journal-Lancet **64**: 1, 1944.
14. Salomonsen, L., and Nygaard, K. K.: Acta paediat. **27**: 209, 1939.
15. Shapiro, S., Redish, M. H., and Campbell, H. A.: Proc. Soc. Exper. Biol. & Med. **53**: 251, 1943.
16. Warner, E. D.: West. J. Surg. **50**: 408, 1942.
17. Webster, A., and Fitzgerald, J. E.: S. Clin. North America **23**: 85, 1943.

Discussion

DR. AUGUSTA WEBSTER.—The conclusions of both of these essayists are interesting and instructive. Dr. Potter finds, after a careful review of the mortality figures, that "no demonstrable decrease in infant or fetal mortality can be expected to follow the routine administration of vitamin K to all women during labor," and she seems to have proved her point. Dr. Schmidt has added a study on the effect of vitamin K using aquinone. His findings are similar to ours at the County Hospital, including the observation that certain barbiturates lower the prothrombin level of the newborn infant, and that this hypoprothrombin state may be relieved by the administration of vitamin K to the mother during labor.

In these papers, as in all others in the literature to date, there is no demonstration of why some babies with a low prothrombin level bleed, while others do not. It remains for the physiologists to give us the answer. It is certainly true that many babies with a prolongation of prothrombin time do not bleed, but on the other hand, all of the bleeding babies on whom we took the prothrombin level showed a depression below the average physiologic drop of the second and third postnatal days.

To establish a daily normal for babies by the micro method of Kato and Poncher, the blood of 50 babies was checked at the end of each of the first 6 days of life. The averages were 73.8, 59.1, 59.5, 67.3, 75, and 78.9 per cent of normal.

Fifty babies whose mothers had vitamin K orally were also checked daily, and the average prothrombin levels found to be 78.7, 89.3, 87.8, 94, 94.7, and 99.8 per cent. Fifty-four babies whose mothers had synthetic K intravenously or intramuscularly were checked with a daily average of 86.5, 84.7, 91.5, 94.1, 98.7, and 103.6 per cent.

Twenty-eight babies whose mothers had barbiturate analgesics were checked by the same method, and daily averages of 53.1, 38.6, 38, 51.4, 71.1, and 75 per cent were found.

Twelve babies whose mothers were given barbiturate analgesics, and vitamin K during labor were checked, and the averages were 86.4, 87.6, 91.4, 95.4, 98, and 101 per cent.

The neonatal drop in prothrombin is more striking than the figures show. Three babies were excluded from the control series because of clinical bleeding, plus a low prothrombin which made immediate administration of vitamin K seem desirable. One of these had coffee-ground emesis on the second day when the prothrombin was 56 per cent. The other two had continuous bleeding from heel punctures, one on the third day with a prothrombin of 15 per cent, and the other on the fourth day with a prothrombin of 19 per cent. After the administration of vitamin K the prothrombin time rose and the symptoms subsided.

Of the thirty control babies whose mothers had barbiturates, five were withdrawn from the series because of hematoma and continuous oozing at the site of heel puncture. Four of the mothers had received 7½ grains of pentobarbital sodium and one had been given 1 Gm. of sodium Amyl-bromoallyl; all of these improved after the administration of vitamin K.

Seven other babies were called to our attention because of bleeding. These were not in the series originally and, therefore, we do not know what the prothrombin was until

after the onset of symptoms. One baby on the third day had bleeding from the nostrils, and subconjunctival hemorrhages, a coarse tremor, and cyanosis of the face. There was no clot in five minutes. The diagnosis made by the Department of Pediatrics was hemorrhagic disease of the newborn with possible cerebral hemorrhage. One baby had coffee-ground vomitus on the third day with a prothrombin of 36 per cent. One baby showed vaginal bleeding and jaundice on the third day with a prothrombin of 35 per cent. One baby on the fourth day showed a large fluctuant bluish mass on the right cheek, and petechial hemorrhages on the palate with a prothrombin of 10 per cent. A diagnosis of hemorrhagic disease of the newborn was made by the Department of Pediatrics. One baby showed evidence of intracranial damage on the fifth day with a prothrombin of 21 per cent. Another showed palatal bleeding on the fifth day, and a prothrombin of 10 per cent. One showed coffee-ground vomitus on the fifth day, and a prothrombin of 15 per cent. All showed marked increase in prothrombin and cessation of bleeding promptly after administration of vitamin K intramuscularly.

Eight additional babies developed neonatal hemorrhage and were studied:

CASE 1.—The infant had coffee-ground emesis on the second day, with a prothrombin level of 54 per cent. One hour after it received 10 mg. of vitamin K intramuscularly, the prothrombin rose to 66 per cent and in the next two days was 85 and 88 per cent, respectively.

CASE 2.—A large cephalhematoma was noted on the second day. The prothrombin level was 18 per cent and 10 mg. of vitamin K was given. The next day the prothrombin level was 84 per cent.

CASE 3.—Forty-eight hours after birth, this infant's cord began to bleed and was retied. A hematoma formed on the proximal portion and the blood did not clot in five minutes. Ten milligrams of vitamin K were given, and one hour later the prothrombin level was 30 per cent, and the infant was bleeding from the original heel puncture. Another 10 mg. of vitamin K was given, and an hour later the prothrombin level was 48 per cent, the following day it was 67 per cent, and two days later it was 92 per cent.

CASE 4.—On the third day numerous petechiae appeared on the face, neck, and scalp, and subconjunctival hemorrhages were found in the right eye. The prothrombin level was 37 per cent, vitamin K was given, and on the next three days the level was 77, 83, and 92 per cent, respectively.

CASE 5.—This infant vomited bright red blood on the third day, and the prothrombin level was 30 per cent. After vitamin K was given, the level rose to 93 per cent, and was 100 and 103 per cent on the next two days.

CASE 6.—Hematuria appeared on the third day. The prothrombin level was 26 per cent. One hour after vitamin K was given the level rose to 56 per cent. The next day it was 62 per cent, and 80 per cent on the following day.

CASE 7.—Epistaxis occurred on the third day and ecchymoses about the left eye. The prothrombin level was 18 per cent, vitamin K was given, and on the following day the level was 78 per cent.

CASE 8.—On the third day bleeding occurred from excoriations on the chin, and the prothrombin level was 14 per cent. One hour after the administration of vitamin K, the level was 24 per cent, and on the following day 80 per cent.

During the eighteen months of the study which Dr. Fitzgerald and I conducted at the Cook County Hospital, 5,370 normal infants were delivered. Forty-four of these developed signs of hemorrhage in the first few days of life, an incidence of 0.82 per cent. Of these, 42 babies were born of mothers who had received no vitamin K, an incidence of 1.18 per cent for this group. Two were born of mothers who had received some form of vitamin K during labor, an incidence of 0.11 per cent.

We do not believe that it was an accident that 42 out of 44 neonatal hemorrhages occurred in patients who had no vitamin K.

It seems reasonable that fetal mortality as Dr. Potter has shown, would not be altered by the use of vitamin K, since the vast majority of causes of fetal mortality could not be affected by its use. It does seem, however, that infant morbidity may very well be affected. Babies admittedly show a decrease in prothrombin content from the second to fifth day of life, and it is significant that hemorrhage of the newborn infant, when it occurs, appears during this period of lowered prothrombin content.

It is true that prolongation of prothrombin time has not been shown to be a direct cause of hemorrhage, and that many babies with low prothrombin level do not bleed;

however, in our observations every bleeding baby in which the prothrombin level was checked showed a marked depression. The low level appears to be a factor. It seems probable also that there may be unobserved, but not necessarily unimportant, internal hemorrhages in infants (possibly cerebral) which might be lessened if vitamin K were routinely given to women at the onset of labor. Since a striking drop in prothrombin level occurs when the barbiturates are given, it seems that vitamin K is desirable when these analgesics are used.

As Dr. Schmitz has emphasized, in order that the infant may have the advantage of the vitamin K during the trauma of labor, it is preferable that the vitamin be given to the mother before or at the onset of labor, rather than to the infant after birth.

BLOOD PRESSURE IN NORMAL PREGNANCY

GEORGE J. ANDROS, M.D., ANN ARBOR, MICH.

(From the Department of Obstetrics and Gynecology, University of Michigan Hospital)

THE importance of following blood pressure in antepartum patients has been emphasized by obstetricians since the perfection of a simplified sphygomanometer by Riva Rocci in 1896. Development of hypertension during the period of gestation is recognized as distinctly abnormal.

Precisely what constitutes normalcy in range and trend of blood pressure during uncomplicated pregnancy has been investigated by a number of workers and reported in the American, English, and foreign literature.[1-37]

Many of these reports are based upon isolated observations or computed averages of variable numbers of readings collected more or less at random during pregnancy. A few investigators have sought to follow blood pressure through the three trimesters by means of serial readings.

In 1925 Simons and Rasmussen[3] of the Mayo Clinic reported the blood pressure changes in 27 patients from the second month to term—with several more, seen less often. They noted a slightly irregular but gradual rise in systolic, diastolic, and pulse pressures during pregnancy. Their charts show figures of 107/65.3 at the second month, 116/65.2 at the sixth month, and up to 119/73.7 at term. During the six weeks following delivery there was a gradual fall to 109/66.6.

Somewhat similar results were published by Imaz[35] of Buenos Aires in 1939. In his 120 cases the average systolic pressure climbed irregularly from 90 to 116 at term. The diastolic pressure varied between 65 and 70 in the first two trimesters and remained close to 80 throughout the third trimester.

Hare and Karn[36] of the London Royal Free Hospital reported in 1929 an investigation of blood pressure, pulse rate, and response to exercise during normal pregnancy. They found the average systolic blood pressure during pregnancy to be lower than the average of nonpregnant women, with a tendency to a lower pressure in the middle period than in earlier weeks, and a slight rise in the last three months. Diastolic pressure during pregnancy was not found to be significantly different from that of nonpregnant women. It was somewhat lower during the first six months and exhibited a steady rise during the seventh month to a maximum in the last month that was higher than the mean for women not pregnant.

Intrapregnancy mean figures were derived from 456 readings made on 106 patients and on readings from 145 other individuals seen once or twice only. Means for nonpregnant women were calculated from readings on young "welfare women," laundry workers, and female medical students.

Cornell[14] in 1929 reviewed 1,000 consecutive cases of pregnancy followed through the three trimesters, calling those cases "normal" whose average systolic pressure remained below 129– as contrasted to other "potentially toxic" and "toxic" groups. In the "normal" group there was a slight, gradual systolic and diastolic drop from the second to the fifth months, and then a rise to a term pressure that was not significantly higher than that found in the first trimester. There was no more than 5 mm. Hg difference between the highest and lowest systolic and diastolic readings at any time during pregnancy.

An impressive study was made by Henry[15] of McGill, published in 1936. The author observed 618 cases through pregnancy and concluded that there is a "marked" fall from the nonpregnancy average in diastolic pressure and a rise in pulse pressure, with some evidence for believing that systolic pressure is lower in the pregnant state.

This conclusion was based upon a comparison of Henry's general average figure of 120/67 for all readings made during pregnancy with a "normal" figure of 120/78, the latter pressure being derived from tables of normal values for women between 20 and 40 years of age prepared by the Sun Life Assurance Company of Canada.

In following this author's average figures according to month and week (during the last month) of pregnancy, little variation from the general average is seen. A low systolic pressure of 115 is noted during the third month and a high of 124 at term. Diastolic pressure is lowest in the fourth month with a reading of 65 and highest in the first week of the ninth month with 72.

Another study is that of Cohen and Thomson[18] of the Boston Lying-In Hospital and published in 1939. In 51 cases these workers found "a definite tendency for average systolic and average diastolic pressure to decrease from the fourth to the ninth lunar month, and to increase during the tenth." The figures accompanying this report reveal a diastolic drop of impressive magnitude, but the decrease in systolic pressure is slight.

Material Used in This Study

This study seeks to determine the range and trend of blood pressure through the course of normal pregnancy. It is unique in that all cases studied presented one or more pressure readings taken prior to the onset of the pregnancy.

The cases included in this series number 300. Two hundred and ninety-three of the patients (97.7 per cent) were white. Six Negro women and one Chinese complete the list. The average age for the group as a whole was 27.7 years. There were 160 primiparous patients (53.3 per cent) and 140 multiparas (46.7 per cent). It should be mentioned that a large majority of the records studied were those of private patients, University Hospital nurses, and other Hospital employees, and former University of Michigan students—in general from the "middle income" bracket.

Each case record included in this study met three requirements:

1. The record presented at least one prepregnancy blood pressure reading taken with the subject in good health.

(There were 661 prepregnancy readings in the study, an average of 2.2 per patient. The length of time between the prepregnancy reading and the onset of the last menstrual period preceding the pregnancy ranged from two days to five years, the time interval being less than one year in 125 out of the 300 cases and less than three years in 225 cases.)

2. The antepartum record of each patient included at least one blood pressure reading taken during each of the three trimesters of the pregnancy.

(There was a total of 3,391 intrapregnancy readings, an average of 11.1 for each patient. In the University of Michigan Maternity Clinic and private obstetrical service, every patient is requested to present herself for a checkup examination once a month for the first six calendar months of the pregnancy, twice a month in the seventh month, and once a week in the eighth and ninth months.)

3. The patient was entirely free at all times during gestation from evidence of toxemia of pregnancy—through sign, symptom, and routine laboratory examination. A systolic pressure of 140 or a diastolic pressure of 90 at any time during the pregnancy eliminated the patient from this study, even in the absence of any other sign or symptom of toxemia.

While blood pressure tends to vary in the same individual under the influence of such factors as recent activity, emotional stress, etc., we feel that a degree of correctness and comparability between prepregnancy and intrapregnancy figures can be expected, since

all readings in this study were taken under similar conditions and with mercury sphygmomanometer.

Intrapregnancy reading were made in the course of routine antenatal checkup examinations. The prepregnancy readings were taken while the patient was in good health during a routine periodic or pre-employment physical examination—made in the University Hospital or University Student Health Service exclusively.

Methods of Analysis

The data obtained from the first 300 case records meeting the above requirements (chosen after an examination of approximately 2,000 records bearing the diagnosis of "Normal Pregnancy") were analzed by three methods—as follows:

1. The average systolic, diastolic, and pulse pressures for the whole group were computed for each calendar month (and week in the late stages) of pregnancy. These figures were compared with the average prepregnancy pressures for the entire group.

2. The average systolic, diastolic, and pulse pressures for the whole group were computed for each trimester as a unit, and then compared with the average prepregnancy pressures.

3. Each patient's average systolic and diastolic pressures according to trimesters as units were computed. With prepregnancy pressures in each case considered as "zero," deviations for each trimester in every case were calculated and from these the average deviations for the whole group.

Summary of Analyses

The 661 prepregnancy readings in the 300 cases yielded an average "normal" blood pressure of 114.6/72.6 (pulse pressure 42).

This pressure is lower in both systolic and diastolic components than the "normal" 120/78 used by Henry in his study. Robinson and Brucer,[38] studying the blood pressure of 3,015 women having readings under 140/90, concluded that the mean figures for women between 25 and 29 years of age were 109.4/66.7 (pulse pressure 42.7).

In comparing the average prepregnancy pressure (systolic, diastolic, and pulse) for the group as a whole with the average intrapregnancy figures for the entire group calculated according to calendar month—or week—of pregnancy (Table I and Fig. 1), no significant deviation in systolic pressure was noted at any time during gestation.

The greatest variation from the prepregnancy "normal" was a rise of 2.15 mm. Hg in the last week before term. The lowest average systolic pressure was 113.08 (second week of eighth month), and the highest was 116.74 (last week before delivery).

Diastolic pressures were consistently lower than the "normal" in the first six and one-half months of pregnancy, but the drop was not at all marked. Deviations ranged from 2.64 to 4.15 mm. Hg below the prepregnancy figure. There was no significant variation from

TABLE I. AVERAGE PRESSURES CALCULATED ACCORDING TO CALENDAR MONTH OF PREGNANCY

	SYSTOLIC	DIASTOLIC	PULSE
Prepregnancy	114.59	72.58	42.01
CALENDAR MONTH OF PREGNANCY			
1	114.00	69.56	44.44
2	114.53	69.85	44.68
3	114.63	68.43	46.20
4	114.43	69.94	44.49
5	114.50	68.98	45.52
6	113.30	69.18	44.12
7 (early)	114.71	68.55	46.16
7 (late)	116.16	70.65	45.51
8_1	114.96	71.08	43.88
8_2	113.08	69.98	43.10
8_3	114.75	71.96	42.79
8_4	115.15	72.31	42.46
9_1	114.32	72.25	42.07
9_2	115.52	73.24	42.28
9_3	113.88	72.98	40.90
9_4	116.74	75.66	41.08

the prepregnancy diastolic pressure in the last two and one-half months of gestation. Average diastolic readings ranged irregularly from 68.43 at the third month to 75.66 at the last week before delivery.

Average pulse pressure increased with the diastolic fall noted above, varying between 46.20 at the third month down to 40.90 at the third week of the ninth month.

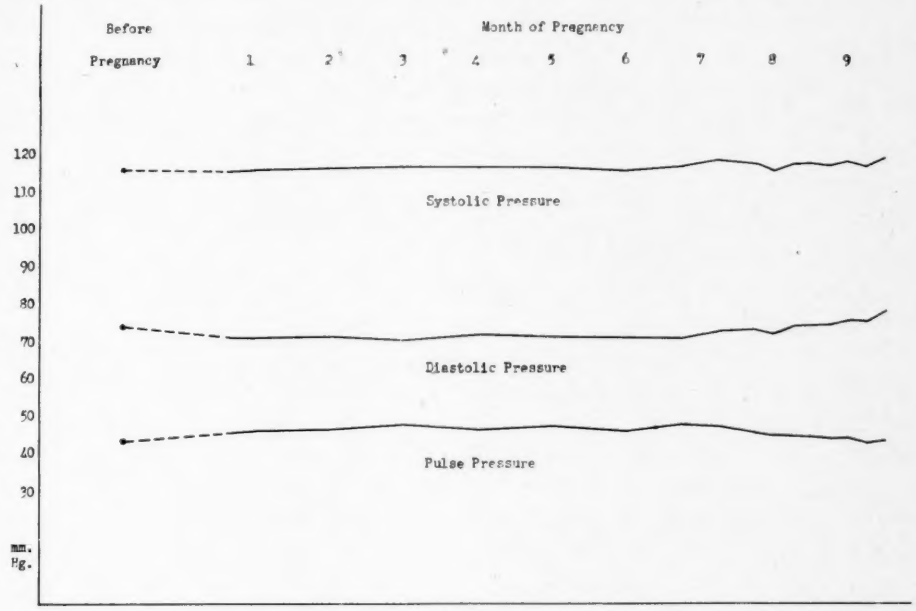

Fig. 1.

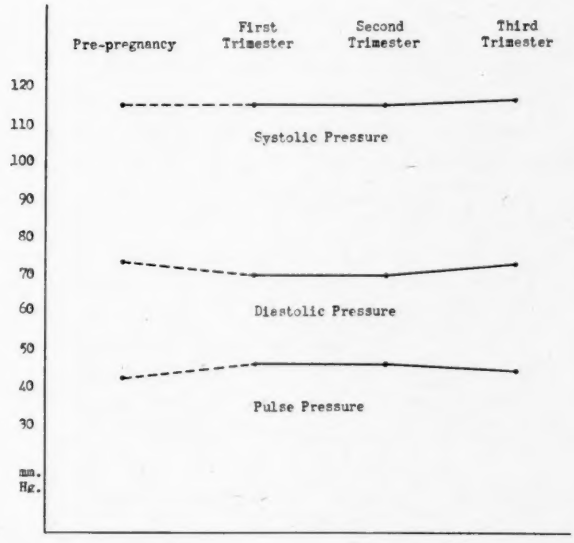

Fig. 2.

TABLE II. AVERAGE PRESSURES CALCULATED ACCORDING TO TRIMESTERS

	SYSTOLIC	DIASTOLIC	PULSE
Prepregnancy	114.59	72.58	42.01
First trimester	114.61	69.02	45.59
Second trimester	113.97	68.99	44.98
Third trimester	115.17	71.97	43.20

When average intrapregnancy pressures for the group as a whole computed according to trimester were compared with the average prepregnancy figures (Table II and Fig. 2), the absence of variation in systolic pressure was striking. No more than 0.62 mm. Hg deviation from the prepregnancy average was found in any of the trimesters. As compared with the prepregnancy figure of 114.59, average systolic pressures of the three successive trimesters were 114.61, 113.97, and 115.17.

The slight fall in diastolic pressure during the first two trimesters again was evident in this method of analysis. The first trimester average diastolic figure (69.02) was 3.56 mm. Hg lower than the prepregnancy figure, and that of the second trimester (68.99) lower by 3.59 mm. Hg. In the third trimester, average diastolic pressure (71.97) was only 0.65 mm. Hg deviated from the average pressure before pregnancy.

Average pulse pressure again reflected the diastolic fall by rising in the first two trimesters.

Calculating the deviation of each patient's systolic and diastolic pressures (according to trimesters as units) from the average prepregnancy figures of each case (considered as zero), and then computing the average deviation for the group as a whole gives results similar to those seen in the other methods of analysis (Table III).

Again there was no significant difference in systolic pressure in each of the trimesters as compared with the pressures taken before pregnancy. In diastolic pressure the small but consistent drop occurring only in the first and second trimesters amounted in this case to average deviations downward of 3.48, and 3.67 mm. Hg, respectively.

TABLE III. AVERAGE DEVIATIONS

(Computed From the Deviations of Each Patient's Pressure by Trimesters From Each One's Prepregnancy Pressures)

	SYSTOLIC	DIASTOLIC
First trimester	+0.09	−3.48
Second trimester	−0.41	−3.67
Third trimester	+0.23	+0.47

TABLE IV. PROPORTIONS OF CASES SHOWING SOME DEGREE OF DEVIATION (BY TRIMESTER UNITS) FROM EACH ONE'S AVERAGE PREPREGNANCY BLOOD PRESSURE

		SYSTOLIC			DIASTOLIC		
		FALL	NO CHANGE	RISE	FALL	NO CHANGE	RISE
First	No.	162	14	124	204	6	90
Trimester	%	54.0	4.67	41.33	68.0	2.0	30.0
Second	No.	152	10	138	204	20	76
Trimester	%	50.7	3.3	46.0	68.0	6.7	25.3
Third	No.	152	6	142	142	10	148
Trimester	%	50.7	2.0	47.3	47.3	3.3	49.4

It is of interest to note that approximately two-thirds of the patients (204 cases or 68 per cent) in this series exhibited some diastolic fall in the first trimester as a unit, and an identical number in the second trimester, but only an approximate one-half of the patients (148 cases or 49.3 per cent) showed a diastolic pressure fall in both the first and second trimesters. The numbers of cases showing falls or rises in systolic pressure tended to be more equal to each other in each trimester. This was also true for the diastolic pressure deviations in the third trimester. (Table IV.)

Discussion

It has been found in this study of 300 cases of normal pregnancy followed through three trimesters that systolic blood pressure does not vary significantly during any period of gestation, nor does it deviate from what might be considered normal systolic blood pressure for healthy nonpregnant women.

By the three methods of analysis used, diastolic pressure consistently has been found to be slightly lower during the first and second trimesters of pregnancy than during the third trimester or in the nonpregnant state. In the third trimester, diastolic figures are not significantly different from those found before the onset of pregnancy.

Whether or not these small but consistent deviations downward in diastolic pressure noted in the first two-thirds of pregnancy are significant is difficult to state. These may well be within the limits of error arising from the use of an instrument such as the sphygomanometer and from the normal variations in blood pressure. On the other hand, the striking lack of variation in systolic pressure would lead us to consider any consistent variation in diastolic pressure, though small, as being statistically accurate. Theorizing on the etiology of this fall in diastolic pressure during the first two trimesters is beyond the scope of this paper.

The observations presented here should serve indirectly to re-emphasize the fact that any persistent rise in blood pressure during pregnancy should be looked upon with suspicion.

Conclusions

1. Our study reveals that systolic blood pressure does not vary at any time during normal pregnancy from the level for a normal and healthy young woman who is not pregnant.

2. There is evidence that diastolic blood pressure tends to be slightly lower in the first and second trimesters of normal pregnancy than in the normal nongravid state.

3. On the basis of this study it would appear that any persistent, even though slight, increase in either systolic or diastolic pressure during pregnancy should be looked upon as potentially significant.

References

1. Skeel: Am. J. Obst. & Dis. Women & Children **59**: 369, 1909.
2. Newell: J. A. M. A. **64**: 393, 1915.
3. Simons and Rasmussen: Minnesota Med. **8**: 303, 1925.
4. Schulze: Minnesota Med. **3**: 585, 1920.
5. Wiesner: Zentralbl. f. Gynäk. **23**: 1335, 1899.
6. Slemons and Goldborough: Bull. Johns Hopkins Hosp. **208**: 194, 1908.
7. Von Jaschke: Arch. f. Gynäk. **94**: 809, 1911.
8. Fellner: Quoted by Von Jaschke.[7]
9. Schroeder: Quoted by Von Jaschke.[7]
10. Strassmann, E.: Arch. f. Gynäk. **136**: 345, 1929.
11. Ride, L.: Chinese M. J. **52**: 329, 1937.
12. Hinselmann: J. A. M. A. **81**: 515, 1923.
13. Danforth: Am. J. Obst. & Dis. Women & Children **77**: 927, 1918.
14. Cornell, E. L.: Am. J. Obst. & Gynec. 18: 42, 1929.
15. Henry, J. S.: J. Obst. & Gynaec. Brit. Emp. **43**: 908, 1936.
16. Hurst: Trans. Am. Gynecol. Soc. **54**: 153, 1929.
17. Osborn, G. R.: South. M. J. **20**: 710, 1927.
18. Cohen, M. E., and Thomson, K. J.: J. A. M. A. **12**: 1556, 1939.
19. Vaquex, and Nobecourt: Bull. de Soc. d'Obstet. de Paris, 1897 (quoted by de Snoo[20]).
20. de Snoo, K.: Monatschr. f. Geburtsh. u. Gynäk. **57**: 235, 1922.
21. Engelmann, F.: Monatschr. f. Geburtsh. u. Gynäk. **61**: 208, 1923.
22. Schwarz, G.: Arch. f. Gynäk. **135**: 133, 1929.

23. Donaldson: J. Obst. & Gynaec. Brit. Emp. 24: 133, 1913.
24. Litzenberg: Internat. Clinics 4: 141, 1917.
25. Simon, T.: Acta obst. et gynec. Scandinav. 11: 365, 1931.
26. Irving: J. A. M. A. 66: 935, 1916.
27. Faught: Am. J. Obst. & Dis. Women 71: 507, 1915.
28. Hirst: Am. J. Obst. & Dis. Women 71: 507, 1915.
29. Walser, H. C.: J. Michigan M. Soc. 29: 899, 1930.
30. Upshur, J. N.: Virginia M. Monthly 49: 3, 1922.
31. Review of Literature: J. A. M. A. 67: 435, 1916.
32. Kronig, and Futh: Ztschr. f. Geburtsh. u. Gynäk. 51: 249, 1904.
33. Faught, F.: Am. J. Obst. & Gynec. 11: 633, 1926.
34. Culbertson: Trans. Am. Gynecol. Soc. 54: 153, 1929.
35. Imaz: Semana méd. 2: 100, 1939.
36. Hare, D. C., and Karn, M. N.: Quart. J. Med. 22: 381, 1929.
37. Wollman, H.: Geburtsh. u. Frauenh. 2: 42, 1940.
38. Robinson, S. C., and Brucer, M.: Arch. Int. Med. 64: 409, 1939.

CAUDAL ANALGESIA IN OBSTETRICS WITH SPECIAL REFERENCE TO REPEATED SINGLE BLOCKS

Bernard J. Hanley, M.D., and Charles M. Malone, M.D.,*
Los Angeles, Calif.

(From The Department of Obstetrics and Gynecology of the University of Southern California School of Medicine)

IN THE last two years, the use of caudal analgesia in obstetrics has increased markedly. From all parts of the country various investigators have published reports of their experience with this analgesia. The great majority of these reports has been based on the continuous caudal technique as advocated by Hingson and Edwards.[1] Our purpose in presenting this paper is to report the use of caudal block in 1,925 obstetric cases at the Los Angeles County Hospital, from July 1, 1942, to July 1, 1944. Since February, 1944, we have used repeated single caudal block for complete analgesia during labor and delivery in a small series of 152 cases. We will present our observations and results in this small series in detail. The disposition of the 1,925 cases is as follows:

1,343		primiparas (Single block)
316		multiparas (Single block)
68		Continuous caudal
	42	primiparas
	26	multiparas
46		Cesarean section (Single block)
	30	primiparas
	16	multiparas
152		Repeated single caudal block for analgesia and delivery
	101	primiparas
	51	multiparas

Technique and Materials

The patient is placed in the modified Sims' position. If we find it too difficult to give the caudal in this position, we change to the knee-chest position. Our skin preparation consists of a scrub with tincture of green soap, followed by ether, then a final covering with Zephiran solution. A sterile drape is placed over the area and the needle inserted.

A 20 gauge, blunt, stainless steel spinal needle is used routinely. We use a wheal of

*All residents on the obstetric service participated in this work, but special credit is due to Lt. (j.g.) Jack Murietta, M.C., U.S.N.R., now in active service, and Hildegarde Wilkinson, M.D.

the anesthetic agent to alleviate the pain while inserting the needle. Following insertion of the needle, aspiration for spinal fluid or blood is then carefully and repeatedly carried out.

For single injection caudal block for delivery, when the presenting part is "crowning," we prefer 2 per cent procaine. The patient is placed on the delivery table, prepared, the history is checked for barbiturate premedication, and the needle is inserted. A dose of 25 to 30 c.c. of the 2 per cent procaine is given, never more. We feel that a dose larger than this is not necessary. Furthermore, it would be dangerous to both mother and child. It is a rare individual that does not obtain complete relief from this medication. The patient is immediately rolled flat on her back to prevent a one-sided block. The delivery is performed without pain and most often without the patient's knowledge. This routine comprised the great majority of cases in our series.

Repeated Single Caudal Block for Analgesia and Delivery

From February, 1944, to July, 1944, we have given repeated single caudal blocks to patients throughout labor for complete analgesia and delivery. This has been tried before at this institution but without success as the drugs used did not give a sufficient period of analgesia to make repeated single blocks applicable. Shortly after the first of the year we obtained tetracaine (pontocaine) ¼ per cent in physiologic saline. This dilution contains 2.08 mg. of tetracaine to 1 c.c. of solution.

Varying amounts of the tetracaine, with and without adrenalin, were given at different stages of labor. Our first aim was to achieve a safe analgesic agent for both mother and child and then to find the correct proportions that would make the mother as comfortable as possible. We feel that the safety of the mother and child surmounts all other considerations. We also desire to alleviate the pain of childbirth as completely as possible while at the same time not interfering too markedly with the progress of labor.

At the present time, we give the patient 1½ grains of nembutal with 10 grains of aspirin when her contractions become painful. Demerol, 50 mg., in place of aspirin, has been used recently with very promising results. We attempt to evaluate the patient very carefully as to the probable length of time before delivery can be anticipated and also as to the character of her contractions. When she is having regular uterine contractions of moderate intensity of more than thirty seconds' duration and not more than four to five minutes apart, we give her the first caudal block. We prefer that the head be engaged, that the cervix be 40 to 50 per cent effaced and of at least 3 to 5 cm. dilatation. We request the patient to tolerate the pain as long as she can before the first block is given, assuring her that we can make her completely comfortable for the duration of her labor and delivery. The amount of solution injected with the first caudal block varies somewhat with the individual patient and with the experience of the operator. If the patient is a primipara with hard uterine contractions every two minutes, who is 5 to 6 cm. dilated, we give her 25 c.c. of the ¼ per cent tetracaine, with 3 minims of $\frac{1}{1.000}$ adrenalin, in the original injection. If the patient is a multipara, having painful uterine contractions every five minutes, of mild to moderate intensity, and is progressing slowly, we give her 22 to 23 c.c. of the same solution.

We have routinely checked blood pressures in this series of 152 cases. The pressure is taken immediately before the caudal block, immediately after, five minutes after, fifteen and thirty minutes after, and every hour throughout labor; with few exceptions it remained within the range of normal. The patient usually becomes comfortable in five to ten minutes and labor continues; the uterine contractions and fetal heart tones are checked regularly.

The large majority of multiparas are carried through labor and delivery with a single injection. In those cases where a repeat caudal is necessary, because the patient again feels pain, she is prepared, and given a second injection, the usual amount being 20 c.c. If a third injection is given, the amount is also 20 c.c. When the presenting part is on the perineum, the patient is placed on the delivery table and given a last caudal block of 25 to 30 c.c. of 2 per cent procaine. We have found that subsequent injections of tetracaine give less complete and shorter periods of analgesia. Hence, for delivery, we switch to 2 per cent procaine as the anesthetic agent.

The relief from pain with repeated single caudal blocks as employed here is not as complete as that obtained with continuous caudal, as advocated by Hingson and Edwards. We feel it is good psychosomatic medicine to have the patient come out of the analgesia and experience a few painful contractions. She is much more appreciative if you relieve her of pain on two or three occasions than if she is allowed to experience no pain whatsoever.

Results

Outlet or low forceps are used routinely in this teaching institution for all primiparas. We have found, however, that a good percentage of the primiparas and a large majority of the multiparas will deliver spontaneously with fundal pressure. However, as reported by numerous other investigators, the patient has no urge to bear down and use her voluntary expulsive powers. We feel that the normal progress of labor is very definitely interfered with at this point, but not prohibitively so.

We have found that the shortest labor under single caudal block was twenty minutes. The longest labor under repeated single blocks was fourteen hours and thirty-five minutes. The average duration of labor in multiparas after the first block was two hours and one minute. In primiparas, the average length of labor, after the first caudal block, was five hours and seventeen minutes. We are convinced that the first stage of labor is definitely shortened under caudal analgesia. The second stage is prolonged, however, due to the absence of the voluntary expulsive powers of the mother. The length of the third stage appears unchanged, while the blood loss seems less. Occiput posterior positions are more common, due to the relaxation of the "pelvic sling" and loss of the voluntary expulsive powers. Occiput posterior positions were found in 11.9 per cent of our cases. However, rotation of the head was greatly facilitated by caudal block.

The average length of analgesia produced by a single caudal block, with ¼ per cent tetracaine with adrenalin, was two hours and thirty-one minutes in primiparas and one hour and fifty minutes in multiparas. In each case, several patients delivered before the period of analgesia wore off, thus shortening the average length of analgesia. This was particularly true among the multiparas. The period of analgesia was considerably shortened when adrenalin was not added. The length of labor was approximately the same with or without adrenalin. The average number of single caudal blocks given to each patient in our series was: for primiparas, 2.7; for multiparas 1.3.

In this series of 152 cases there were no fetal or maternal deaths attributable to caudal block. There were no infections of the skin, subcutaneous tissue, or deeper structures. There were no serious accidents. A blood pressure drop below 90 mm. systolic occurred in three of the patients. This was entirely asymptomatic and was treated simply by elevating the legs in two instances and by giving a small dose of ¾ grain ephedrine sulfate to the other. About 8 per cent of our patients complained of some pain over the sacral region, but this disappeared in a few days. In one case, a very inconsequential pain persisted for ten weeks. There were no known complications or undesirable side results reported by the patients at their postpartum examination, six weeks after delivery.

Eleven major surgical procedures were carried out under single caudal block, using ¼ per cent tetracaine. All patients were definitely poor anesthetic risks. There were four extraperitoneal cesarean sections carried out with very good anesthesia. Two vaginal hysterotomies on eclamptic patients in very poor condition were done successfully. Four low cervical cesarean sections were performed, one of which was in a patient with a very severe pre-eclamptic toxemia of pregnancy. There was no maternal or fetal mortality attributable to the anesthesia.

In this entire series of 1,925 patients, from July, 1942, to July, 1944, there have been no maternal deaths from any cause; and no fetal deaths

attributable to this anesthesia. There have been no infections of any kind. One serious accident occurred, which we will describe in detail:

This patient was given a single caudal block for delivery, 25 c.c. of 2 per cent procaine being used. All precautions had been taken to aspirate carefully for blood or spinal fluid. Neither was obtained. Within five to seven minutes, the patient had ceased to breathe and became a dusky hue. Normal blood pressure was maintained for fifteen minutes then dropped to shock level. Artificial respiration was carried out and stimulants were given for one hour. At about that time she began to breathe spontaneously. Fetal heart tones became somewhat rapid, but the patient was delivered of a crying baby following recovery. Anesthesia was present to level of the second rib. Lower extremities were completely paralyzed for two hours. Both the mother and child fully recovered. We assume that a massive spinal injection was given. Failure to obtain spinal fluid on aspiration is to be explained by the probable collapse of the membranes around the needle point upon attempts to aspirate.

The percentage of successful analgesia was 96 per cent in the 1,925 cases. We considered a caudal block successful if it was not necessary to add additional anesthetic agents.

Indications

We have used caudal block more or less as a routine measure in obstetric cases at this hospital. We have maintained a very strict list of contraindications, which will be given later. There are conditions in obstetrics in which caudal block is probably the anesthetic agent of choice. These conditions are: premature labor, heart disease, and pulmonary disease. There are times also when it is most desirable in toxemias of pregnancy, soft-part dystocia, and cesarean sections.

Contraindications

We believe that caudal block should not be carried out in surroundings lacking adequate materials and personnel to combat every possible type of accident. It should not be used in the case of hypertonic, hysterical, or uncooperative patients, and those not desiring it. It should not be used in patients with severe anemia or those bordering on exhaustion; likewise, not in those patients with abruptio placentae or placenta previa; nor in any case where the diagnosis is uncertain or where disproportion is suspected. If the patient gives a history of idiosyncrasy to the anesthetic agent; any deformity of the spine; or if there is any evidence of pyodermia, again its use should be avoided. This list does not necessarily include all the conditions which would prevent its use. More experience with it will probably bring some new ones.

Complications

Subdural Injection.—It is a definite contraindication to administer a caudal block if spinal fluid is aspirated before the injection or during the injection of the anesthetic fluid. This is one of our potentially most dangerous accidents and should be carefully guarded against. In our series of 1,925 cases, we knowingly aspirated spinal fluid in four cases.

Intravenous Injection.—If free blood is aspirated repeatedly, the attempts at caudal block should be stopped. Ordinarily, one can turn the needle, readjust it, wait two or three minutes, test again, and inject if no blood is aspirated.

Blood Pressure Drops.—Prophylaxis is most important in the selection of your cases; however, if blood pressure drop does occur, elevation of the lower extremities and the use of ephedrine sulfate will usually combat it successfully.

Infection.—Infection may occur as a subcutaneous abscess, osteomyelitis, epidural abscess, meningitis, septicemia, or as a simple skin lesion. Treatment consists for the most part of prophylaxis. Absolute sterile technique is essential.

Broken Needles.—One should not give caudal block if he is not familiar with the bony landmarks and technique. The regular 20 gauge flexible spinal needle, which we use, is quite safe. Never insert the needle to the hub, nor put on undue strain. The patient is always cautioned to lie still.

Comment

Repeated single caudal blocks for analgesia and delivery, using ¼ per cent tetracaine with small amounts of adrenalin added, has shown much promise in the small series of 152 cases. We intend to continue this type of analgesia until we can draw more abstract and useful deductions from its use. We feel that this form of analgesia is more advantageous than continuous caudal block for the following reasons:

The average length of labor under continuous caudal analgesia in a total of around 10,000 cases has been shown in primiparas to be between six and eight hours. In multiparas the average length of labor under similar conditions is around two hours. The average length of analgesia we obtained with single caudal injections with ¼ per cent tetracaine was two to three hours. The average number of caudal blocks that it was necessary to give in our series was less than three. Therefore, we feel it more advantageous to give one, two, or three single caudal blocks for complete analgesia and delivery than to use the continuous caudal.

Hingson[2] and Hodges[3] and others have written that continuous caudal analgesia when carried out for periods of over seven to eight hours becomes increasingly more unsatisfactory, with complications increasing rapidly. We can administer two, and at the most three, single caudal blocks which will produce caudal analgesia for seven to eight hours. The complicated continuous caudal technique is not necessary.

Continuous caudal analgesia requires the constant attendance of the obstetrician or trained anesthetist, as we very definitely feel this responsibility should not be placed on a nurse. Single caudal blocks do not require this constant attendance, if the obstetrician is readily available.

Economically, a trained anesthetist must charge a large fee to attend an obstetric patient for six to eight hours checking the continuous caudal. Single caudal blocks can be given in three minutes. We must be practical in our attitude if we expect caudal block to be used extensively.

The patient can move at will with single caudal block. Examinations of all kinds can be made with ease, while under continuous caudal they are much more difficult.

The chances for infection are much less with single caudal block. One can maintain a very aseptic technique for three to five minutes, but for eight hours it is more difficult. There is a constant avenue for bacteria to the epidural space with the continuous caudal technique. We feel that merely covering the tray with a sterile towel and using care not to touch the barrel of the syringe is not enough to prevent infection.

The chances for broken needles are much less with single caudal blocks. Hingson and Edwards[4] in an earlier report listed twelve broken needles in a series of six hundred cases. Lyons and Hansen[5] report four broken needles, of the latest type, in their series of two hundred obstetric cases in which continuous caudal analgesia was used. We have not had a broken needle in 1,925 cases.

The chances for massive subdural injections are much less with single caudals. We never insert the needle deeper than is necessary to enter the caudal

canal, while in the continuous setup the needle must be inserted to the hub in every case. With the needle in place for several hours and the patient moving about, perforation of the dura or blood vessel could easily occur, with a serious accident resulting on subsequent injections.

It is much easier technically to insert an ordinary steel spinal needle into the caudal canal than the malleable ones used in the continuous caudal.

Backache is a very common complaint in those patients receiving continuous caudal. About 8 per cent of our patients complained of transitory sacral discomfort.

One-sided analgesia is very seldom seen with repeated single caudal blocks. The patient can lie flat on her back or turn as she wills. Often with continuous caudal, the patient will have a level of anesthesia on the dependent side with continuous cramps on the upper side.

The continuous caudal equipment is quite difficult to manage when the patient is being moved. A long tube protrudes from the back of the patient. One must be careful not to pull on that tube the slightest as the needle will be displaced or the tubing pulled from the needle hub. The accompanying tray of bottles, syringes, etc., which one must keep sterile, is difficult to manage for eight hours.

No special equipment is needed for single caudal blocks. The equipment for continuous analgesia is inexpensive, but is quite prone to become defective with use. Any well-supplied hospital will have the material necessary for single caudal blocks.

Summary

We have presented the results obtained in a series of 1,925 cases with caudal block. A technique for complete analgesia and delivery under repeated single caudal injections with ¼ per cent tetracaine has been described. This technique has been compared with continuous caudal analgesia, as advocated by Hingson and Edwards.

Conclusions

1. Single caudal block technique has a definite place in the practice of obstetrics. Its use is varied. It can be used as a single block for delivery or it can be repeated throughout labor for analgesia and delivery. Our results with caudal anesthesia for obstetric surgery are very encouraging.

2. Single caudal block, when given by an experienced individual under proper conditions, can be as safe or more so than other forms of analgesia.

3. Caudal block administered correctly will give as good results as any other form of analgesia.

4. The use of interrupted single caudal blocks for analgesia and delivery gives promise of effectiveness and safety for mother and child.

5. Caudal anesthesia in obstetrics should be limited to well-equipped institutions, which have a full-time resident or a teaching staff.

References

1. Hingson, R. A., and Edwards, W. B.: J. A. M. A. **123**: 538, 1943.
2. Hingson, R. A.: Am. J. Obst. & Gynec. **47**: 718, 1944.
3. Hodges, W. R.: J. A. M. A. **125**: 336, 1944.
4. Hingson, R. A., and Edwards, W. B.: Anesthesiology **4**: 181, 1943.
5. Lyons, H., and Hansen, F. M., Jr.: Am. J. Obst. & Gynec. **47**: 105, 1944.

1930 Wilshire Boulevard

CONTINUOUS CAUDAL ANALGESIA IN OBSTETRICS ON TRIAL*

ROY E. NICODEMUS, M.D., F.A.C.S., LEROY F. RITMILLER, M.D., AND
LEWIS J. LEDDEN, M.D., DANVILLE, PA.
(From the Department of Obstetrics, Geisinger Memorial Hospital)

IN THE past two years numerous claims and counterclaims have been made for continuous caudal analgesia in obstetrics. In our opinion a fair analysis of this new method can be determined only if it is judged by the same standard as other types of analgesia.

We were one of the first groups to become interested in this new method and, consequently, received instruction in the technique as devised by Hingson and Edwards in the first course conducted at the Philadelphia Lying-In Hospital.

At the Geisinger Memorial Hospital we have endeavored for the past fifteen years to give adequate relief for pain in childbirth. This has entailed the use of numerous methods, always with the idea in mind of giving maximum relief of pain, consistent with safety to both mother and child.

We selected for this comparative study the last 500 consecutive deliveries prior to the institution of caudal analgesia, and the first 500 consecutive cases managed with continuous caudal analgesia.

In our clinic, which operates with a full-time staff in group practice, three physicians devote full time to the handling of all obstetric cases admitted to the hospital. We felt, therefore, that a fair and honest study comparing continuous caudal analgesia with other methods previously used would be enlightening and of some significance, especially since it correlates the results in 1,000 consecutive deliveries managed only by the Obstetrician-in-Chief and his two associates in a period less than two years.

For the sake of brevity in the remainder of this discussion the 500 consecutive deliveries prior to the use of caudal analgesia will be designated as Group I. All of these cases received sedation in the form of sodium pentobarbital in the amount of 4½ to 7½ grains. In addition, those cases requiring stronger sedation were given an oil ether mixture by rectum, and in all instances inhalations of ethylene or nitrous oxide were given at the actual time of delivery and repair.

The other 500 consecutive deliveries receiving caudal analgesia will be spoken of as Group II.

According to Table I it will be noted that the incidence of primiparas and multiparas in the two groups is almost identical, which is especially advantageous from the standpoint of comparison.

It was our impression before attempting this analysis that labors conducted under caudal analgesia were shorter in duration. Our figures in Table II have disproved this, and instead we have found that the average length of labor in primiparas in Group II was approximately one hour longer than in Group I; likewise in multiparas we discovered that labors in Group II averaged two hours longer than in Group I.

*Presented before a meeting of the Philadelphia Obstetrical Society, Dec. 7, 1944.

TABLE I. PARITY

PARA	GROUP I	GROUP II
Primipara	222	224
Multipara	278	276
Total	500	500

It may be asked by some: Why use a technique that tends to lengthen labor? Our reply is that it probably is a minor disadvantage if time is the unit of measure in obstetrics, but the strange part is we were convinced caudal labors were shorter until our figures proved otherwise, and the reason we thought they were shorter was that the patient was awake, comfortable, pleasant, and cooperative. It is when a patient is restless, uncoordinated, and irrational from her medication that the hours seem endless to the attending doctor and nurses.

TABLE II. AVERAGE DURATION OF LABOR

PARA	GROUP I	GROUP II
Primipara		
1st Stage	8 hr. 56 min.	9 hr. 34 min.
2nd Stage	1 hr. 34 min.	1 hr. 56 min.
3rd Stage	3 min.	3 min.
Total	10 hr. 33 min.	11 hr. 33 min.
Multipara		
1st Stage	5 hr. 59 min.	7 hr. 15 min.
2nd Stage	46 min.	1 hr. 26 min.
3rd Stage	4 min.	3 min.
Total	6 hr. 49 min.	8 hr. 44 min.

Let us now consider the incidence and results of occiput posterior positions in these two groups. In Group I a diagnosis of occiput posterior was made 94 times as against 122 times in Group II. Our study shows that spontaneous rotation took place in 86 out of 94 cases in Group I, or in 91.5 per cent, whereas only 69 rotated spontaneously out of a possible 122 in Group II, an incidence of 56 per cent. This, we believe, can be accounted for on the basis of diminished intensity of uterine contractions and relaxed birth canal where caudal technique is employed. It is, we believe, an accepted fact that strong uterine contractions forcing the vertex down against a resistant pelvic floor is the greatest aid to spontaneous rotation. Therefore, when these factors are altered we must expect the reverse to be true, and consequently, as shown in Table III, in Group I assistance to correct occiput posteriors had to be carried out in only 8.5 per cent of the cases as compared with 43.5 per cent in Group II.

In comparing Groups I and II as to types of delivery in Table IV, it is quite evident that the incidence of operative delivery is greatly increased where caudal analgesia is used. Our figures show that spontaneous delivery occurred 113 more times in the group in which caudal analgesia was not used; also low-forceps delivery was resorted to 103 more times with caudal analgesia. Midforceps delivery in the two groups showed the greatest contrast with twenty such deliveries under caudal analgesia as against three in Group I. This rather

TABLE III. OCCIPUT POSTERIOR

	GROUP I		GROUP II	
OCCIPUT POSTERIOR	(NO.)	(%)	(NO.)	(%)
Spontaneous rotation	86	91.5	69	56.5
Forceps rotation	5	5.3	20	16.5
Manual rotation	3	3.2	33	27.0
Total	94	18.8	122	24.4

marked increased incidence of operative deliveries with caudal analgesia, to our minds, indicates that the force of the uterine contractions are reduced in intensity; also, the expulsive force of the abdominal musculature is lost where this technique is employed. At the same time, it cannot be said to be a condemnation of the method, for in its favor we have a greater relaxation of the pelvic floor resulting in much less permanent trauma to these tissues. The shock of delivery is almost negligible and the blood loss is insignificant, all of which are major factors in the consideration of the patient.

TABLE IV. TYPES OF DELIVERY

TYPE	GROUP I (NO.)	GROUP I (%)	GROUP II (NO.)	GROUP II (%)
Spontaneous	312	62.0	199	39.2
Low forceps	160	31.8	263	52.0
Midforceps	3	0.6	20	3.9
Breech	28	5.6	25	4.9
Total	503 (3 sets of twins)		507 (7 sets of twins)	

We would like to call attention at this point to the ease with which breech deliveries were accomplished under caudal analgesia as compared with other types of anesthesia we have used. It is an established fact that breech deliveries have always carried a much higher mortality for the baby than almost any other type of delivery, largely because of the rigidity of the pelvic floor musculature preventing the necessary rapid delivery of the infant before asphyxia occurs. All these difficulties are overcome where caudal analgesia is employed since the soft tissues of the birth canal are so completely relaxed that they offer almost no resistance to extraction of either the breech or the head and this is all accomplished wihout placing the patient under deep surgical anesthesia.

TABLE V. FETAL COMPLICATIONS

COMPLICATIONS	GROUP I	GROUP II
Apnea—lasting a few minutes	102	10
Stillbirths	13	5
Neonatal deaths		
a. Full-term	2	1
b. Premature	5	6
Total	122	22

In Table V we have a notable contrast in fetal complications, especially marked in apnea lasting a few minutes after birth. This was found to be ten times more common in Group I where the barbiturates and rectal ether were used, necessitating resuscitation with oxygen in a fair percentage of cases. In Group II apnea and resuscitation were negligible factors since caudal analgesia has no effect upon the respiratory center of the baby. Again a notable factor was the much higher incidence of stillbirths in Group I as compared with Group II. This, we feel, can be explained on the basis of too intense and too frequent uterine contractions in Group I, occasionally resulting in intrauterine asphyxia of the baby, whereas in Group II we have already acknowledged that uterine contractions are of less intensity under caudal analgesia. Under the heading of neonatal deaths it is noted that there were seven in each group, which offers no point for comparison or discussion.

Probably the most important thing to consider in the use of any new procedure in obstetrics is whether or not the incidence of maternal mortality and morbidity can be reduced. In our series as shown in Table VI we had thirty-

seven cases of morbidity in Group I or an incidence of 7.4 per cent as compared with twenty-nine cases or 5.8 per cent in Group II. In neither group were there any mortalities. The margin of difference in morbidities in the two groups is small, yet we feel it is great enough to be of some significance. When we consider that operative procedures were 58 per cent more frequent in Group II where caudal analgesia was used, it becomes evident that we may have to revise our opinion that morbidity and mortality are proportionate to the incidence of operative interference in obstetrics. There are, we believe, certain other factors, such as minimal blood loss, absence of anesthetic shock, and prompt postpartum response of the patient as shown by immediate ability to ingest food and fluids, all of which tend to offset the increased hazards of operative procedures.

TABLE VI. MORBIDITY AND MORTALITY

	MATERNAL MORBIDITY	MATERNAL MORTALITY
Group I	37	0
Group II	29	0

In the discussion of analgesia for the obstetric patient, one's chief concern is the extent of relief of pain to that particular individual in her labor. It is to the best interests of each one of us for the patient to be able to say that she did not suffer long hours of pain and exhaustion, and yet we have all experienced the humiliation of having given some medication that we felt quite sure would give the desired good effect, only to find that the patient's reaction was entirely contradictory.

In our series we were unable to evaluate Group I concisely as to the percentage of good relief simply because a large portion of cases receiving barbiturates and rectal ether are uncooperative for hours due to narcosis. Even though they are not interrogated as to their relief of pain until the day after delivery, they often cannot differentiate between adequate and inadequate relief.

In Group II we have an entirely different standard by which to judge. The patient's sensorium is not affected; she is completely and entirely conscious at all times so that she is able and willing to give full cooperation throughout the entire labor and delivery. Consequently, our figures show that in the 500 cases delivered with caudal analgesia 469 had complete relief, 16 had partial relief, and 15 were failures. In other words, 93.8 per cent of this group had total analgesia, 3.2 per cent had only partial relief, and 3 per cent had none. Therefore, in our experience, to date, caudal analgesia has given a higher percentage of complete relief to the mother than any other method or combination of methods we have employed.

To some of you it may seem facetious to mention the morale and dispositions of the various personnel in the obstetric department. Yet, in all truthfulness, we can attest to the fact that this is true and of considerable importance. The nurses in the labor rooms enjoy caring for the caudal analgesia patients, whereas in other types of analgesia they are often harassed and exhausted trying to manage a restless, boisterous, uncooperative type of patient through her labor. Then, too, it is not necessary to hurry about trying to locate or call an anesthetist to control the patient for the final delivery and repair. No other anesthesia is required. The patient is simply moved to the delivery table at the proper time, delivered, and repaired if necessary while carrying on a pleasant conversation. Such conditions are bound to improve the dispositions not only of the nurses but of the doctors as well.

Still another fact well worth discussing and one which was mentioned earlier in the paper is the improved postpartum response of the patient receiving caudal analgesia. These patients are nearly always ready to eat a little food and drink fluids immediately after delivery, in fact many of them are able to do so during the course of their labor, all of which aids greatly in maintaining normal blood chemistry and consequently fluid and nutritional balance.

By reason of this prompt postpartum response, the patient may be moved to her room within a few minutes of the time of her delivery. The husband is amazed that he may see his wife so soon and delighted when he sees that she is awake, responsive, and happy, and apparently none the worse for her experience.

It is not enough to say that the method is too dangerous because of possible needle breakage, infection, penetration of the subarachnoid space, etc. We had no needle breakage in our series. One patient did develop a cellulitis superficial to the sacrum which accounted for one of our morbidities, but she made a complete recovery without complication. The subarachnoid space was penetrated in three different instances in the series, but this was promptly recognized and the procedure was discontinued. It is not a foolproof technique, but, on the contrary, one that needs careful thought and judgment and a willingness on the part of the doctor to remain close to the patient.

Summary and Conclusions

To summarize, we must in all honesty point out that our analysis shows that where caudal analgesia is used the labors are longer. Uterine contractions are of less intensity, the expulsive force of the abdominal musculature is lost. Occiput posterior positions rotate less often, and operative deliveries are increased. On the other side of the scales we can place the advantages of this technique, such as easier and safer breech deliveries, a lower incidence of stillbirths, a lower maternal morbidity, diminished blood loss with delivery, less permanent damage to the birth canal, and a pleasant, happy, cooperative patient. In other words, we have not yet found the utopian type of obstetric analgesia, but we are convinced that continuous caudal analgesia is a distinct advance in this field and an excellent method to add to the armamentarium of every obstetrician.

Discussion

DR. ROBERT A. HINGSON, PHILADELPHIA, PA.—Continuous caudal analgesia should be put on trial by all obstetricians who still manage women in pain throughout labor and delivery. It is not a technique of any two physicians or of Philadelphia physicians, but a procedure that has been developed through step-by-step progress of physicians from many parts of the world. It represents a frontal attack against the site of origin of obstetric pain itself. In many instances it eliminates the need for the "smoke-screen" of anesthesia and amnesia from anesthetic and narcotic drugs with which physicians have attempted to control pain.

As Dr. Nicodemus has pointed out, continuous caudal analgesia can prolong labor. I have seen it stop the processes of labor. By frank discussion of such disadvantages, we can protect both the patient and the baby from its misapplication. On the other hand, we have seen cases in which labor was accelerated by the use of this method.

Dr. Nicodemus did not indicate the upper level of analgesia in those cases in which he attributed the prolonged labor to caudal analgesia. Our observations have been that the forces of labor are impaired and eventually made ineffectual in prolonged high caudal blocks above the segmental levels of thoracic 8. Ideally, caudal block should not extend above the umbilicus (T-10). Nevertheless, on some occasions, unexpected high caudal block results from the average dosage of 30 c.c.

The revealing comparison of the improved condition of the baby managed with caudal analgesia should lead us to conclude that this method of pain relief is an indicated one even though it be an imposition on the physician's time.

During the past two years, 600 physicians have come to Philadelphia from all parts of the world to observe our technique of continuous caudal and, later, continuous spinal analgesia. Recently we sent questionnaires to these physicians and they reported the management of 46,000 labors and deliveries under this technique.

This altered obstetrics has presented a sociologic problem which demands attention both by physicians and by hospital authorities. It is an obstetric, as well as an anesthesiologic problem. We think the paper of Dr. Nicodemus is a landmark along the way which points toward adequate analgesia and pain relief in obstetrics even though physicians lose sleep in bringing about this effect.

DR. THADDEUS L. MONTGOMERY, PHILADELPHIA, PA.—Dr. Nicodemus has pointed out several advantages of the caudal method over the barbituric acid analgesia which he had formerly used. These, in respect to the lack of depression of maternal or fetal respiration, and in respect to greater relief of the mother, are generally accepted. I was a little disappointed that so little was said of the difficulties of insertion and administration of the caudal anesthesia, and nothing of the sequelae of caudal anesthesia. Most of those who have given even a few caudal anesthesias, even after careful instruction by competent anesthetists, have experienced some difficulties. Not a few patients have returned following caudal anesthesia with some local complaint.

Aside from the technical difficulties, and the complications of minor or moderate severity, the crux of the situation seems to lie in the problem of how far we can go with any method of anesthesia in obstetrics which inhibits the nautral powers of labor. Certainly, thus far, no satisfactory substitute has been found for the natural fashion of delivery, including the dilatation of the cervix by recurrent contractions of the uterus in the first stage, and propulsion of the fetus through the birth canal by the combined efforts of the uterus and abdominal muscles in the second stage. The longer I am in obstetric practice, the more impressed I am with the favorable condition of mother and child after a so-called natural labor, and with the fact that the earlier we interfere in the mechanism of labor, the greater are the complications that will result.

When we began using so-called prophylactic forceps, we applied them only when the scalp was visible and the perineum and vulva were projected forward in front of the advancing head which had molded itself into the outlet of the pelvis. Year after year we seem to be interfering somewhat earlier in this mechanism. Now, with the advent of caudal anesthesia and of spinal anesthesia in obstetrics, we rather impertinently apply our forceps with the head in midpelvis, or in low pelvis, and complete in a few minutes what Nature ordinarily takes an hour or two to accomplish. That such procedures can be done consistently even by competent obstetricians, without unnecessary damage to the mother or to the baby, is not possible to believe.

I feel quite in agreement with the opinion that the regional methods of anesthesia, that is, spinal, caudal, and local, offer many advantages over central or systemic anesthesia. The greatest of these, of course, is the lack of anoxemia in the baby and the freedom from inhalation anesthetic accidents in the mother. In these directions, the regional methods of anesthesia represent quite a step forward. It would appear also that the more peripherally administered the anesthesia, the safer the effects. In this direction, therefore, the injection of a local anesthetic agent in the perineum during the final stage of delivery and for the repair of episiotomy, combined with "whiffs" of nitrous oxide and oxygen or ether, is one of the very safest of anesthetic methods, and one which has achieved and should continue to receive a large following in obstetric practice.

Some months ago, from the material of our clinic at the Temple University Hospital we presented a comparative study of caudal and spinal anesthesia in obstetric practice. We found that each of these two methods presented certain advantages and certain disadvantages. The spinal method was administered more readily and more certainly, and with a higher degree of success. It seemed somewhat safer in that we had comparatively little reaction and the anesthesia was always given in the delivery room when the entire personnel for delivery, including doctors, anesthetists, residents, and nurses, was present. It was given over only a comparatively short period of time, so that close observation was necessary for only an hour, or an hour and a half. In some few cases, however, the spinal anesthesia was followed by a

moderate postpartum bleeding, and in no case did the anesthesia appear to have as profound a relaxing effect on the pelvic floor and perineum as did the caudal anesthesia.

There was one detrimental feature, however, which was common to both methods. All sense of perineal pressure was obtunded, and the head never advanced beyond the pelvic floor unless the patient was consistently and continuously coached to bear down. Even then a spontaneous delivery was only accomplished in the multiparous patient. In a number of cases we found ourselves doing so-called low forceps delivery, which was anything but a simple extraction of the fetal head through the vulva. As has recently been mentioned by Baptisti, many of the forceps necessitated drawing the head down beneath the symphysis pubis and dilating the pelvic floor and perineum with rather strenuous traction. This, we feel, is not good obstetrics. I am inclined to believe that anyone who uses either the caudal or the spinal anesthetic method, and who analyzes his cases honestly, will acknowledge that there are quite a few deliveries of this type.

DR. W. ROYCE HODGES, CUMBERLAND, MD.—Our work is done in a general hospital with no interns or residents. Nevertheless, since Oct. 3, 1942, over 500 obstetric cases have been delivered under continuous caudal analgesia. We have also used continuous spinal anesthesia in all forms of operative work, in abdominal and pelvic surgery, and favor it. Under the circumstances in which we are forced to work, however, I feel that continuous spinal analgesia must be limited to those few obstetric patients who cannot for some reason be given continuous caudal analgesia.

When using continuous caudal for pain relief in our labor cases, the patients are under constant observation by one of three graduate nurses who have been trained by us. With these nurses in attendance we feel perfectly safe in leaving these patients throughout the remainder of their labor, it being understood that we are constantly on immediate call. Our successful results have been in direct proportion to the proper placing of the caudal needle. Of our first 300 cases, 222 were completely satisfactory. Forty-two of the remaining 78 cases were classified as failures, and by far the majority of this group failed because of faulty insertion of the needle. Of the remaining 36 patients, in the light of our more recent experience, at least half were due to failure to insert the needle properly. In short, most of our disappointments with the method have been due not to any faulty principle of the method, but to personal failure in technique.

Another pitfall which we are learning to avoid through experience is that of too early administration. In primiparas especially, if one waits until the patient is crying for relief of pain after the administration of an average dose of the usual barbiturate, or a small early dose of morphine or demerol, providing there is progressive dilatation of the cervix and descent of the presenting part, then is the time that continuous caudal analgesia can be expected to give ideal results. From the standpoint of time, continuous caudal of four to five hours' duration in primipara has been the maximum optimum time for our patients. We have had patients carried over a period of seven to twelve hours and longer with good result, but this is not the rule.

One other point is that our experience in the increase of operative deliveries is very similar to that of Dr. Nicodemus. I know that I have been responsible for the death of two babies because of faulty judgment in trying to rotate the head too soon. At the present time my feeling is that if a persistent posterior head offers too much difficulty in manual or instrumental rotation, it is wiser for me to let up on the caudal, allow the patient to bear down with her returning pain, and in this manner greatly aid in the rotation.

To condemn this method because of a few personal failures is more than unfair. In our hands, under entirely different circumstances from which others work, we find it a very favorable method and we will continue to use it until we find something better.

DR. NICODEMUS (closing).—In regard to the question that Dr. Montgomery brought out, I can only say that I know of no sequelae in our series following the use of caudal. We do feel, however, that within a few hours after delivery the patients are likely to develop overdistended bladders due to the fact that they have not regained the sensation in this region. Hence we make it a point to have our nurses inspect the abdomen frequently after delivery and catheterize one or more times during the first twelve to twenty-four hours when necessary.

What has been said about nursing requirements is very true, but I think as time goes on more doctors will be available and the hospitals will again have adequate nursing service. However, I see no reason why a resident trained in this particular method could not be called upon to give the caudal analgesia at the proper time in labor. We do it in our institution and it works very satisfactorily.

THE USE OF FINE CHROMIC CATGUT FOR POSTPARTUM PERINEAL REPAIR*

EDWARD G. WATERS, M.D., F.A.C.S., JERSEY CITY, N. J.
(From the Margaret Hague Maternity Hospital)

THIS is a record of experiences with perineotomy repairs using very fine chromic catgut sutures. The number of cases providing the data is sufficiently large and carefully followed to permit a statistical appraisal of the material, and other data experimentally obtained are pertinent. While the primary object is to observe tissue reaction and healing and the patient's pain response to the very fine suture used, due recognition is given the varied factors which act in any delivery as agents influencing perineal repair and healing. Very fine catgut sutures are not commonly used for postpartum repairs of birth tract injuries or incisions although the literature of the past few years indicates a growing awareness of its value in surgical technique.

While an exhaustive exposition of the principles indicating the use of very fine catgut material is not proposed here, a consideration of present-day types of fine chromic sutures as compared to former and older brands is certainly in order.

The function of a suture is to obtain hemostasis and hold in apposition the divided structures sufficiently long to permit adequate wound healing before loss of effective suture strength through absorption. Catgut is mainly collagen prepared from the submucosa of the jejunum of the sheep. As natural or plain catgut, it has a fairly rapid rate of absorption and therefore is seldom applied except where rapid loss of strength is unimportant. To prolong the absorption time, these collagenous strands are chromicized and made uniform in smoothness and tensile strength. The storage solution must cause a minimal degree of tissue irritation.

An emplaced suture acts essentially as a foreign body and provokes the reaction one might expect. The dilatation of the capillaries and veins and polymorphonuclear leucocyte reaction, extravasation of plasma cells and plasma is to be expected. The action upon the suture is to soften it, fracture it, and prepare it for absorption. The enzymatic proteolysis from polymorph degeneration begins and the macrophages proceed to digest and phagocytose the strands. Since all of these processes interfere with the appearance and activity of fibroblasts, it is obvious that the most desirable suture is one which evokes the *least* leucocytic response and permits *earliest* proliferation of fibroblasts. In properly receptive tissues, at the end of a week the suture should be surrounded by new capillaries, young fibroblasts with developing collagenous fibers, a minimal number of leucocytes, and yet retain some of its initially inherent tensile strength. Excessive tissue reaction with collection of serum, the onset of infection with increased numbers of leucocytes, cellular necrosis from lacerated or badly bruised wounds, contused and ecchymotic areas, all interfere with the physiologic process described. Many systemic disturbances, especially those associated with emaciation, starvation, general debility, diabetes, etc., interfere with wound healing. It has been experimentally determined that chromic

*Read before a meeting of the New York Obstetrical Society, Jan. 9, 1945.

catgut produces a lesser foreign body reaction than plain catgut and that smaller sizes of chromic catgut, while producing a minimal degree of tissue reaction, retain tensile strength proportionately much longer that larger sizes. A consideration of the available experimental data therefore indicates the *use of the smallest chromic sutures possible* with due consideration of the need for initial tissue coaptation. It has been demonstrated unquestionably that more closely applied sutures of smaller sizes give sounder wounds that those of large chromic catgut placed at greater intervals. One may therefore conclude that properly chromicized catgut of fine gauge is the correct material to use from a theoretic standpoint: first, because smaller-sized needles are used with resulting lesser damage to the punctured tissue; second, the mass of foreign material lodged in the wound is reduced; third, the knot mass is smaller; fourth, unfavorable tissue reaction is diminished, with prolongation of the effective tensile strength of the suture; fifth, there is less superfluous tensile strength in the finer chromic sutures which in itself provides an effective restraint upon strangulation of tissue by the operator.

All of these considerations designate a fine type of chromic suture material as the proper one to employ where absorbable sutures are to be placed in tissue, consistent with the local need for tissue approximation.

The chromic catgut material throughout the series reported in this paper was No. 0000 chromic catgut, the gauge of which is approximately standardized at 0.007 with average tensile strength of 2 pounds.

Experimental Data

At attempt was made to determine the frequency of suture fraying, rate of absorption, and residual tensile strength of strands of No. 0000 chromic catgut remaining in the perineal tissues three, four, five, six, and seven days. Several free strands were placed in non-lacerated perineums of patients and removed at intervals from the third to seventh days, to compare the effects upon the suture material over that period.

Reference to Fig. 1 shows the tensile strength of the suture material as determined immediately upon the withdrawal of the suture strands from the perineums of patients in whom they had been planted after normal spontaneous deliveries without perineotomies. Although more than 70 perineums were used, data could be recorded on few more than 40 individuals because of technical difficulties encountered. Many strands were removed during perineal care, during replacement of vulvar pads, and often by overattentive nurses, or the strand was retracted into the perineum and could not be recovered. However, 73 strands were recovered at varying times from 41 patients and subjected to examination and determination of tensile strength. It is notable that none of these strands showed any fraying on the third, fourth, or fifth days. Two strands showed fraying on the sixth day, and one showed marked fraying on the seventh.

The tensile strength in the strands removed on the third day varied from 1 pound 4 ounces to 2 pounds 8 ounces. On the fourth day the range was 1 pound 7 ounces to 2 pounds 10 ounces. On the fifth day, 1 pound 3 ounces to 2 pounds 12 ounces. On the sixth day, 1 pound 2 ounces to 2 pounds 1 ounce. On the seventh day, 1 pound 2 ounces to 2 pounds 3 ounces. The average tensile strength for all of the suture strands removed from the third to the seventh days is noted: 1 pound 14 ounces, 1 pound 15 ounces, 1 pound 10 ounces, 1 pound 8 ounces, 1 pound 8 ounces. In other words, there is only an average loss of 6 ounces tensile strength in the same suture material from the third to the seventh day in the postpartum perineum. It is apparent that, while the absorption rate may vary in different individuals, a fair constant may be obtained for any group. Varying individual factors make impossible unit predictions on the time length a given suture will retain tensile strength and resist absorption. But for any large group, an accurate appraisal *can* be made, especially for the early and all-important healing time. It is our belief that fraying of sutures is due largely to careless surgical handling, notably loop ties and suture injury with hemostats and needle holders. This is borne out by the rarity with which fraying was encountered in any of the experimentally placed strands.

The tissue reaction to varying sizes of chromic catgut is well seen in the four photomicrographs (Figs. 2 to 5). The size 0 medium chromic catgut and size 0000 medium chromic catgut were used for the comparative tests. Dogs were anesthetized with intravenous sodium pentobarbital and strands of chromic catgut material were imbedded in the anterior wall of the stomach. At the end of five days, sections were removed and paraffin block sections were obtained of the suture and the surrounding tissue and stained with hemotoxylin eosin. A similar technique was carried out by removing the section of the stomach wall at the end of fourteen days when advanced healing was presumed to have occurred. Study of the section shows the absence of unfavorable tissue reaction about the 0000 strands with early fibroblastic formation. The absence of leucocytic infiltration is notable. In the sections removed at the end of fourteen days for microscopic examination, the size 0 or larger strand is noted to be markedly fractionized with approximately half of the strand absorbed. While fibroblastic infiltration is well advanced, it is not nearly so evident nor clear-cut as with the 0000 catgut where the strand shows no evidence of absorption, no tissue reaction other than active fibroblastic formation.

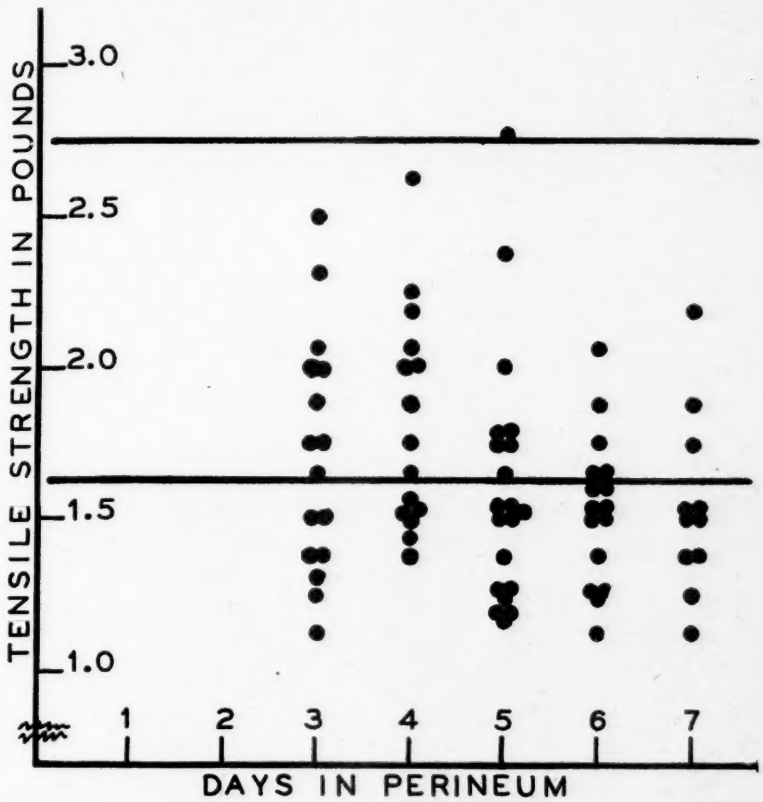

Fig. 1.

Analysis of Clinical Material

The perineal repairs and operations noted in the tables were made with No. 0000 chromic catgut threaded on fine needles. The technique commonly employed was a lock stitch on the mucosa and musculofascial coat of the vagina, and a continuous muscle-approximating suture in the perineum, terminating as a subdermal stitch. Occasionally an interrupted figure-of-eight suture was placed in the depth of the perineal body. When median perineotomies involved the sphincter, the latter with its fascial coat was approximated with two or three interrupted No. 0000 chromic sutures. Nonabsorbable sutures were not used in any instance.

Most of the tables are self-explanatory and require no further elaboration.

The preference for median perineotomy is apparent since it composes more than three-fourths of all the perineal incisions elected. It is well to note that the selection of median perineotomy is often dependent on the type of delivery anticipated as well as the anatomic character of the pelvic outlet and perineum itself.

Fig. 2.

Fig. 3.

Fig. 2.—Size 0 medium chromic catgut embedded in the anterior wall of the stomach of the dog and sections removed for microscopic examination at the end of five days. No evidence of absorption of catgut. Leucocytic infiltration moderate. Early fibroblastic formation.

Fig. 3.—Size 0000 medium chromic catgut embedded in the anterior wall of the stomach of the dog and sections removed for microscopic examination at the end of five days. No evidence of absorption of strand. Leucocytic infiltration absent. Early fibroblastic formation. Note the proximity of intact strand to surrounding tissue. Compare the width of the tissue defect with that made by the 0 strand.

Fig. 4.

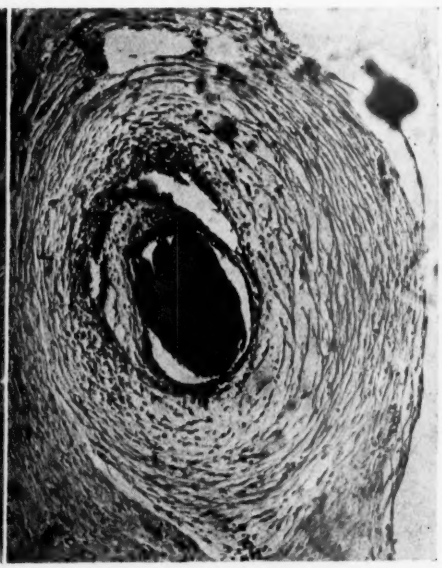

Fig. 5.

Fig. 4.—Size 0 medium chromic catgut embedded in the anterior wall of the stomach of the dog and sections removed for microscopic examination at the end of fourteen days. Fifty per cent of the strand is absorbed. Leucocytic infiltration normal. Fibroblastic infiltration well advanced.

Fig. 5.—Size 0000 medium chromic catgut embedded in the anterior wall of the stomach of the dog and sections removed for microscopic examination at the end of fourteen days. No evidence of absorption of catgut. Leucocytic infiltration absent. Fibroblastic infiltration well advanced.

TABLE I

Primiparas		243		61%
Multiparas		157		39%
Elderly primiparas		31		8%
Previous stillbirths	One	14 cases	3.5 %	4.25%
	Two	3 cases	0.75%	
Previous miscarriages	One	36 (17 had delivered living babies also)		
	Two	5		
	Three or more	4		
Previous cesareans		2		
Previous Manchester-Fothergill		2		

Type of Perineal Injury

Median perineotomy	291	73.0%	76%
Median perineotomy with 3° extension	12	3.0%	
Right mediolateral episiotomy	68	17.0%	
Median lacerations	26	6.5%	

Length of Labor (Hours)

FIRST STAGE			SECOND STAGE		
1-6	175	78%	0-4	328	82%
6-12	138		4-6	22	
12-18	25		6-8	3	
18-24	12		Over 8	6	
Over 24	17				

Anesthesia

Gas-oxygen + ether	269	67.0%	Spinal	67	17%
Ether	18	4.5%	Local block	39	10%
Miscellaneous	6		Intravenous	1	

TABLE II

TYPE OF DELIVERY	NO.	PER CENT	
Normal spontaneous	212		53
Median perineotomy	165	41.2	
Right mediolateral episiotomy	25	6.2	
Median laceration	20	5.0	
3° extension of median	2	0.5	
Low forceps	135		34
Median perineotomy	96	24	
Right mediolateral episiotomy	29	7.2	
With laceration	2	0.5	
3° extension median perineotomy	8	2.0	
Midforceps	27		7
Median perineotomy	17	4.2	
Mediolateral	10	2.5	
Breech	14		3.5
Spontaneous with med. perineotomy	2	0.5	
Forceps to aftercoming head—med. perineotomy	8	2.0	
Right mediolateral episiotomy	4	1.0	
Laceration	3	0.75	
3° extension median perineotomy	2	0.5	
Version and extraction (median perineotomy)	2		
Craniotomy (median laceration)	1		
Face presentation (median perineotomy)	1		
Twins	3 sets		
POSTPARTUM OPERATIONS			
Posterior colpoperineorrhaphy	32	8.0	
Cystocele repair	2	0.5	
Hemorrhoidectomy	4	1.0	

TABLE III

COMPLICATIONS			
1. *Medical*			
Heart disease	3	Diabetes	3
Hyperthyroidism	1	Cholecystitis	1
Pneumonitis	1	Antepartum psychosis	1
2. *Surgical*			
Fibroids	6 } 8 or 2%	Hemorrhoids, infected	2
Fibroids with hemorrhage	2 }	Hemorrhoids, severe	6
Pelvic endometriosis	2	Ether conjunctivitis	1
Chronic mastoiditis	1		
3. *Obstetric*			
Placenta previa	4	Pre-eclampsia	2
Placental abruption	1	Eclampsia (intrapartum)	1
Adherent placenta	2	Sepsis (antepartum)	2
Postpartum hemorrhage	5	Mastitis	2
Postpartum bladder atony	1	Thrombophlebitis	2
Pyelocystitis	2	Polyhydramnios	1
Prolonged rupture of membranes	4		
4. *Incidental Complications*			
Sutures through rectum 2—not cut out, primary healing			
Rectum buttonholed with median incision 2—primary healing			

Fetal Mortality - - - - - - - - - - - - - Total 9 or 2.25%

Autopsies obtained	8	
Dead before labor	3	1 monstrous 2 habitual death of fetus in utero in same patient
Dead during labor	3	1 congenital heart
Neonatal deaths	3	1 congenital heart in premature infant 1 premature with atelectasis, 26 weeks 1 pneumonia at 3 weeks

Weights of babies in third-degree extension of median perineotomy 6, 6-10, 6-10, 7-3, 7-3, 7-6, 7-12, 7-13, 8-1, 8-8, 8-12, 9-3

Sex		*Weights*
Male	192	No significant difference in weights of sexes
Female	211	

TABLE IV.

PAIN RESPONSE*			NO.	PER CENT
No Pain			290	72.5
	DURATION IN DAYS	NO.	TOTAL	PER CENT
Mild	1	11		
	2	36		
	3	13	64	16
	4	4		
Moderate	1	1		
	2	21		
	3	7	34	8.5
	4	4		
	Over 4	1		
Severe	1	1		
	2	4		
	3	2	10	2.5
	Over 3	3		

POSTPARTUM PERINEAL STATUS		
Primary healing	395	98.8
Stitch abscess (no gross infection—clean secondary healing)	3	
Gross infection (no resuture)	1	
Complete breakdown (3° extension)	1	
Fistula	0	
Labial hematoma (3 with local block)	4	

*No pain—complained of no pain. On question said there was none.

Mild—complained of no pain. On question admitted a soreness but no relief requested.

Moderate—complained of some pain or discomfort. No *local* treatment given or requested.

Severe—complained of severe pain, *demanded* relief, usually compresses or local treatment.

TABLE V. END RESULTS—FOUR TO SIX WEEKS POSTPARTUM

		NO.	PER CENT
Number of cases followed		321	80
Nulliparous-type introitus (too tight—7)			
Tight	64	96	30
Normal	32		
Lax	12		3.7
Cystocele	1°	2°	3°
Primipara	5	0	0
Multipara	6	1	1
Rectocele	1°	0	0
Primipara	1	0	0
Multipara	4	0	0
Prolapse		2°	
Multipara		2	

Thirty-two multiparas presenting relaxed posterior walls had corrective postpartum operations. There were no complications in this group incident to the use of fine chromic suture material. Experiences with the patients suffering third-degree extensions indicate no valid reason for using nonabsorbable sutures in this group.

The *most significant results* in this study are to be found in patient pain response, the incidence of primary healing, the rarity of infection, and the end results as noted four to six weeks postpartum. In my experience with perineal incisions, lacerations, or operations, an incidence of over 72 per cent of patients with *no postoperative pain response* is notable. Many were multiparas who had previously had perineal repairs with other and heavier types of suture materials. Recent pain experiences should be most acute, yet with few exceptions such patients recorded discomfort and pain following former perineotomy as having been much more severe. Since pain is a subjective symptom which can be calibrated only by the sufferer, the pain response is charted in conformity to the explanatory key. This is as accurate a record as one may obtain, since the patient makes it herself.

The postpartum perineal status, however, is a different matter, for here we have objective findings permitting constant interpretation. Ninety-eight and eight-tenths per cent of these wounds healed by primary intention with no excessive or notable tissue disturbance. These included many in the moderate or severe pain groups. There was only one gross infection in the entire series and one complete breakdown. The latter occurred in a median perineotomy wound with third-degree extension which became grossly infected subsequent to the employment of local anesthesia. While we do not expect perineal infections to be commonly seen on any service in the hospital, a listing of three minor and two major perineal infections in a group of 400 patients is regarded as good.

Conclusions

The end results noted on the chart represent a follow-up of 80 per cent of the group studied. It suggests that the use of very fine chromic catgut sutures is followed by primary healing of the incised perineum. Further, when the soft parts are neither excessively overstretched by the fetus nor damaged by instrumentation, a nulliparous type introitus may be looked for as the end result in most parturient patients. The results designate primary posterior colpoperineorrhaphy as a good procedure to follow in multiparas with relaxed structures.

It is our conviction that a consideration of the theory of wound healing, experimental data of others and in our own lesser efforts involving the use of fine chromic suture material and the clinical data derived from the study of 400 patients in whom this type of suture material was used, gives evidence to our belief that it is the proper suture material to use for postpartum perineal repairs.

I wish to express my thanks to Dr. Adeline Pendleton for assistance in the compilation of the experimental data. Also to Dr. R. Clock of Davis & Geck, Inc., for supplying the needed apparatus.

39 GIFFORD AVENUE

THE RH FACTOR IN OBSTETRICS*

JACOB HALPERIN, M.D., F.A.C.S., MENDEL JACOBI, M.D., F.A.C.P., AND ALVIN DUBIN, B.A., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology and the Department of Pathology of the Beth-El Hospital)

ENOUGH data and facts have by now been accumulated since the discovery of the Rh factor by Landsteiner and Wiener[1, 2] and the subsequent work by Levine and coworkers[3-6] to show the important relationship of erythroblastosis and the Rh factor, as well as the cause of most intragroup transfusion reactions in women who are pregnant, or who have recently delivered.

With this constantly accumulating evidence of the important role of the Rh factor in pregnancy, we decided to examine our histories to appraise the value of the routine determination of the Rh factor in all pregnant women. We reviewed all the obstetric cases in the maternity division of the Beth-El Hospital for a period of eighteen months, covering the entire year of 1943 and the first six months of 1944.

During this period of eighteen months, 3,885 women were delivered (Table I). These cases do not include pregnanies under four and one-half months' gestation. Up to that period they are not admitted to our obstetric department.

TABLE I. OBSTETRIC CASES REVIEWED FOR AN EIGHTEEN-MONTH PERIOD, 1943, TO JUNE, 1944, BETH-EL HOSPITAL

Total number cases delivered		3,885
Stillbirths, all causes		94
	Males 55	
	Females 39	
Stillbirths, cause designated, but other than erythroblastosis		21
Stillbirths, cause unknown		73
	Males 46	
	Females 27	
Total number live births		3,791
Total number that developed jaundice or any form of erythroblastosis		40
	Males 26	
	Females 14	
Male-female ratio almost 2:1		

Of the 3,885 deliveries there were 94 stillbirths. Deducting from this number all traumatic deliveries, and those where the cause could be rather definitely assigned, such as toxemias, ablatio placenta, prolapsed cord, large fibroids numbering 21, there still remained 73 fetal deaths of unknown causes, ranging from five months' gestation to full term. Of the 94 stillbirths, 55 were males and 39 females. However, of the 73 unexplained deaths, 46 were males and 27 were females, giving a percentage of 63 per cent for males to 37 per cent for females. As the normal ratio of births in the hospital is about equal for both sexes, the uneven ratio in the stillbirths may be of significance. We shall refer to this again later in the paper.

Of the total number of 3,791 live births for the same period, 40 of the newborn infants developed erythroblastosis in some form, ranging from moderate jaundice to the most severe form, from which the baby ultimately died. This is slightly over 1 per cent. Twenty-six of these were males and 14 were females, a ratio of almost two to one.

*Read before the Brooklyn Gynecological Society, Oct. 6, 1944.

TABLE II. ANALYSIS OF ERYTHROBLASTOSIS DEATHS, 1943-1944, BETH-EL HOSPITAL

Total number deaths		18
Autopsies performed		10
	Males 9	
	Females 1	
Autopsies not performed		8
	Males 6	
	Females 2	
Total male-female ratio 5:1		

Ten of the male erythroblastotic babies died, a percentage of 40 per cent, while only one of the female erythroblastotic babies died, a percentage of 7 per cent, the ratio of male deaths over females being almost six to one (Table II). Of the eleven fatal cases, ten came to autopsy. Only in one of these cases was the mother Rh positive; all the rest were Rh negative. In this one case, the baby and the father were also Rh positive. The erythroblastosis in this case can be explained by the mother being type O, and the baby type A. Other investigators have had similar experiences with reference to erythroblastosis in cases in which both mother and baby have been Rh positive.[7, 8]

This finding in erythroblastosis, that the proportion of males is far greater than females, and that the prognosis for a female recovering from erythroblastosis is much better than for a male, is a new phase.

That stillbirths of unknown cause were more frequent in males than females was not entirely new to us. For the past several years we have observed it clinically; but that the actual figures should be so striking was a surprise. We decided, therefore, to check with another source, and examine the records of another institution. Dr. Silik Polayes, attending pathologist of the Cumberland Hospital (Brooklyn), was kind enough to place his pathologic and clinical records at our disposal. We reviewed 103 of his cases with a clinical or autopsy diagnosis of erythroblastosis. Of this group of cases, 51 were from the Cumberland Hospital and 52 collected from various other sources. As the resultant findings were almost identical in both groups, we shall present the figures of both groups together (Table III).

Fifty-seven of the 103 cases of erythroblastosis died but did not come to autopsy; 43 of these were males and 14 females, a ratio of more than 3:1. On 13 stillbirths, autopsies were performed, and of these, 7 were males and 6 females, the proportion almost even; but in the autopsies of 17 neonatal deaths, there were 14 males, and 3 females, a ratio

TABLE III. ANALYSIS OF RECORDS OF ERYTHROBLASTOSIS CASES FROM THE CUMBERLAND HOSPITAL, PROSPECT HEIGHTS HOSPITAL, AND OTHER SOURCES*

Number of case records analyzed			103
Clinically diagnosed, died, and not autopsied			57
	Males 43		
	Females 14		
Ratio of males to females		3:1	
Autopsies performed			30
Autopsies on stillbirths	13		
	Males 7		
	Females 6		
Autopsies on newborns that died during neonatal life	17		
	Males 14		
	Females 3		
Ratio of males to females almost		5:1	
Clinically Diagnosed Cases of Erythroblastosis that recovered			
	Total number 16		
	Females 12		
	Males 4		
Female-Male ratio (reversed)		3:1	

*The case records were furnished through the courtesy of Dr. Silik Polayes, pathologist to the Cumberland and Prospect Heights Hospitals, Brooklyn, N. Y.

of almost 5:1. These figures coincide with our own findings. Only 16 of the 103 cases recovered. and it is noteworthy to point out that of the 16 cases, only 4 were males, exactly the reverse ratio. This suggests a greater severity of the disease when it occurs in the male, and the much greater chances for a female recovering from erythroblastosis than a male.

If in a still larger series of cases the same findings maintain, we would have to seek another factor to explain the greater severity of the disease in males. It is difficult to explain it on a sex-linkage basis. Wiener and Landsteiner[9] conclude from observation and study of families that the Rh factor is not sex linked, and that the distribution of it is the same in both sexes as well as in the four blood groups.

Research would probably have to be pursued with the thought in mind that there may be another genetic factor not yet known, which is sex linked.

Before we instituted the routine determination of the Rh factor in the obstetric department, one maternal mortality occurred due to a transfusion of Rh-positive blood to an Rh-negative patient, and one near fatality for the same reason. In the first instance a transfusion of 500 c.c. of properly typed and cross-matched blood was given, without immediate reaction, to a multipara who was admitted because of placenta previa and bleeding. A cesarean section was performed. She delivered a male with erythroblastosis. Subsequently the Rh factor in the mother was found to be negative. She ran a course similar to acute nephritis, developed uremia, and despite all efforts died on the twelfth day. The second case was a primipara who was delivered with forceps and suffered lacerations with profuse bleeding. Plasma was administered on the delivery table; the next day she was given a transfusion of 800 c.c. of whole blood, properly typed and cross-matched. She had an immediate and severe reaction with constricting pain in the chest. The erythrocyte count next day was 1,250,000, with a hemoglobin of 28 per cent. Nitrogen retention products appeared in the blood. An Rh factor determination showed her to be negative. Subsequent transfusions were given with Rh-negative blood and the patient recovered.

In view of the literature being so replete with pertinent facts concerning the Rh factor in obstetrics, and the accumulated evidence of our own investigation, our obstetric department early this year inaugurated the routine typing and determination of the Rh factor in all women attending our prenatal clinic, and urged all members of the staff to do likewise on their private patients.

The following is an analysis of the first consecutive 500 obstetric patients on whom the Rh factor was determined (Table IV). Where the Rh factor

TABLE IV. ANALYSIS OF 500 CONSECUTIVE PRENATAL RH FACTOR DETERMINATIONS IN PREGNANT WOMEN AT THE BETH-EL HOSPITAL

Total number obstetric cases delivered		500
Rh positive		434
Rh negative		66
Incidence of Rh-negative cases	13.2%	
Incidence of erythroblastosis in the newborn delivered of Rh-negative mothers:		
Number of cases delivered		35
Stillbirths and those newborns that developed erythroblastosis		23
Incidence	65.7%	
Stillbirths		5
Neonatal deaths		2
Males 6 Females 1		
Male-female ratio 6:1		
Cases still undelivered		31

was found to be negative the factor was also determined in the husband when possible.

Of the 500 consecutive determinations we found 66 Rh- negative women, an incidence of 13.2 per cent. This percentage is within the range of other investigators.[12, 13]

To date, 35 of the 66 Rh–negative women have been delivered, and, of these, 23 showed some form of erythroblastosis symptoms. This represents 65.7 per cent of the total Rh-negative patients.

Males again predominated in these erythroblastotic newborn infants, 18 being males and 5 females. Not only were the males predominant, but they represented the most severe types. Four of the male infants died, but none of the females. These findings are in complete conformity with those in the series of cases examined by us, from other sources, and quoted previously.

For the purpose of brevity we included under the term erythroblastosis all cases of moderate jaundice, anemia, icterus gravis, icterus hemolyticus, erythroblastosis, and hydrops fetalis. It may justly be asked as to where we draw the line between physiologic jaundice (icterus neonatorum) and the other forms just mentioned. The fact is that no one has yet drawn a distinct line of demarcation of the so-called physiologic jaundice and the advent of the pathologic state, save for the fact that icterus neonatorum is so termed because it disappears spontaneously. All forms of jaundice and anemias that occurred in our group of 3,791 cases are slightly over 1 per cent. It is hardly logical to apply the term "physiologic" to such a small percentage. It seems more likely that all jaundice in the newborn is pathologic; and that in all likelihood many of these will be explained by the discrepancy of the Rh factor in the mother and the father when routine Rh factor determinations are instituted in all pregnant women, and when erythroblastosis, especially in its mildest forms, is better recognized clinically. Javert[10] gives an incidence of one case of erythroblastosis in 438 deliveries. Polayes gives an incidence of approximately one in a hundred cases.[11] Were we to consider only our fatal cases as the only true erythroblastosis, our incidence would approximate those of Javert.

A word about the treatment. We believe that many more infants would have died in this group had we not commenced treatment early and vigorously. As soon as a baby is born of an Rh-negative mother, a blood smear is made to determine the number of nucleated red blood cells. This is an immediate indication of the possibility of the baby developing erythroblastosis in some form. A count of over 10 should put one on guard. That baby needs a daily blood count for the next few days. A fall in the count, or anemia at the first count calls for immediate transfusion with Rh-negative blood. Transfusion is the anchor sheet. Too often is there too much tarrying and waiting and procrastinating before transfusions are resorted to. By that time there is too much hemolysis and too much liver and brain damage for the infant to overcome.

With this paper we have tried to show the great need for the routine determination of the Rh factor in all pregnant women. Indeed, may we even be bold enough to say that it should be made mandatory like the Wassermann test. We have purposely examined the hospital's records for positive Wassermann reaction, and we did not encounter a single positive case, nor a syphilitic baby in almost 5,000 consecutive admissions. Yet the Wassermann test was done in each of those cases. How much more important then, is the Rh factor determination in the light of the known facts concerning its importance for the mother should she require a transfusion, and for the baby should the mother prove to be of the Rh-negative type.

Summary and Conclusions

1. Discrepancy in the Rh factor is the most potent cause of intragroup transfusion reactions in Rh-negative women, particularly if they have recently been pregnant.

2. Our findings are similar to those quoted in the literature, that, with few exceptions, fetal erythroblastosis results from a mating of an Rh-negative female with an Rh-positive male.

3. New statistics and analyses are here presented which show that the male fetus is more susceptible to erythroblastosis fetalis than the female in the proportion of approximately 3:1, and in fatal cases approximately 5:1. The chances for a female recovering are, therefore, so much greater, thus offering one means of prognosticating the outcome.

4. We urge the adoption, by obstetric institutions, of the routine determination of the Rh factor in all pregnant women.

References

1. Landsteiner, K., and Wiener, A. S.: Proc. Soc. Exp. Biol. & Med. 43: 223, 1940.
2. Wiener, Alexander S.: Blood Groups and Transfusion, ed. 3, Springfield, Ill., 1943, Charles C Thomas, p. 250.
3. Levine, Philip: Yearbook of Pathology and Immunology, 1941, p. 508.
4. Levine, P., Katzin, E. M., and Burnham, L.: J. A. M. A. **116**: 825, 1941; Burnham, L.: Am. J. Obst. & Gynec. **42**: 389, 1941.
5. Levine et al.: Am. J. Obst. & Gynec. **42**: 925, 1941.
6. Levine, Philip: Am. J. Obst. & Gynec. **42**: 165, 1941.
7. Loc. cit.,[3] p. 368.
8. Polayes, Silik: Personal communication.
9. Loc. cit.,[3] p. 250.
10. Javert, Carl T.: Am. J. Obst. & Gynec. **43**: 921, 1942.
11. Polayes, Silik: Personal communication.

RUPTURE OF THE UTERUS*

J. Huff Morrison, M.D., Asst. Surg., P.H.S., and Louis H. Douglass, M.D.
(From the University of Maryland, School of Medicine)

IN 1941 Reese and Linn reported from this clinic on rupture of the pregnant uterus, the number of cases being 34. Since that report there have been seen 11 additional instances of this complication, and it is these 45 cases which form the basis of this report.

That the condition is one of general interest is evidenced by the recent literature upon the subject, in which many phases are considered, and a total of about 450 cases presented. In the tables which follow and in their discussion, these papers will be referred to from time to time and comparisons will be drawn.

The cases forming the basis of this report are from the clinics of the University Hospital, Baltimore, from 1920 through 1943, and from the Baltimore City Hospitals from its inception in 1935 to the same date. The incidence is 1:1,465 deliveries, which is quite close to the combined incidence above.

In this series there were 17 instances of rupture following previous section and we find that four of these had been low cervical operations, in every

*Read at a meeting of the Obstetrical and Gynecological Section, Baltimore City Medical Society, Jan. 12, 1945.

instance the original incision and the rupture being longitudinal. Since the longitudinal approach is more or less routine in our clinics, this is not surprising and should not be construed to mean that the transverse incision of the lower segment is safer. Indeed, should rupture occur in a subsequent pregnancy, the longitudinal tear might be preferred, since it shows less tendency to extend and involve large blood vessels, and lends itself the more readily to repair, a phase which will be considered later.

TABLE I. INCIDENCE

AUTHOR	TOTAL NUMBER OF DELIVERIES	NUMBER OF RUPTURES
Sheldon	47,554	26
Burkons*	17,793	12
Knowles	6,009	12
Dugger	318,103	105
Acken	25,935	15
Davis†	147,625	184
Sadowsky	9,079	13
Eastman	53,574	53
Present report	65,916	45
Totals	691,588	465
Total incidence 1:1,487 deliveries		

*Burkons reported 45 cases of rupture but only gave the number of deliveries for 12 of these.

†Number of deliveries estimated.

TABLE II. CAUSE OF RUPTURE AND MORTALITY

	1920-1929	1930-1939	1940-1943	TOTAL	MOTHER		BABY	
					REC.	DIED	BORN ALIVE	STILL-BORN
Pituitary	0	3	2	5	1	4	0	5
Previous section—classical	2	3	8	13	12	1	7	7*
Previous section—low	0	3	1	4	4	0	3	2*
Version and extraction	3	8	0	11	6	5	2	9
Accouchement forcé	0	0	1	1	1	0	0	1
Labor prolonged	0	0	1	1	0	1	0	1
Labor prolonged with breech	0	1	0	1	0	1	0	1
Labor prolonged with disproportion	0	0	1	1	1	0	0	1
Presentation transverse neglected	1	1	0	2	0	2	0	2
Trauma—abdominal, severe	0	0	1	1	0	1	0	1
Spontaneous	3	2	0	5	1	4	0	5
Total	9	21	15	45	26	19	12	35

*Twin pregnancy.

It would be interesting to report our incidence of rupture following the cesarean operation, but some of our patients go elsewhere for subsequent deliveries, others come to our clinics having had previous sections elsewhere, and, finally, our index does not list patients who have had previous sections. However, a recent survey shows that there have been done at the University Hospital alone, in the time covered by this report, a total of 1,088 cesarean sections with an incorrected maternal mortality of 5.07 per cent. Of this number, 166 had one or more previous sections, but only 23 were operated on for this indication alone. From this it might be reasoned that if we were to adopt the policy of "once a cesarean always a cesarean," we would be almost certain to lose more than the one mother who died in this series.

This patient was a gravida ix, para viii, whose seventh pregnancy was terminated at the University Hospital in 1929 because of a central placenta previa. She should have been sterilized at this time but was not. Her eighth pregnancy was uneventful and delivery normal. The ninth pregnancy went to term and she entered the hospital in early labor. Pains were of poor quality and progress slow. After twelve hours she complained of symptoms which should have been recognized as danger signs but were not, and it was some

thirty-six hours later that the true condition was appreciated and the abdomen opened. The patient died on the fourth postoperative day, the main cause of death being infection. This, of course, was a definitely preventable death.

Implantation of the placenta under the section scar would appear to favor rupture and it is now a rule of both clinics to refer all patients who have had a section to x-ray for placental visualization. If the placenta is reported to be under the scar, the patient is delivered by an elective section.

Another most important factor in the individual who has had a previous section would appear to be multiparity. As pregnancies continue, the uterine musculature becomes definitely scarred and what was at one time a firm union becomes greatly weakened. Or if several (four or more) pregnancies have gone to term and a condition arises requiring section, the chances of an intact scar are greatly lessened. (This was illustrated by the case cited above). It would appear to be conservative obstetrics to sterilize these patients.

The eleven instances of rupture following internal podalic version and breech extraction are disturbingly eloquent of the danger of this operation. During the period covered by this report, version and extraction was done 431 times, the incidence of rupture being 1 in 39. If we were to exclude those cases in which the operation was done on the second of twins, the incidence would be correspondingly greater.

In the five cases in which pituitary extract was responsible for the rupture, it seems only fair to explain that none of these occurred in the hospital, all being referred from their homes after the accident.

The one case of rupture following trauma is interesting and deserves a short summary.

A young primigravida, about thirty-two weeks pregnant, was thrown a distance of some 20 feet from a moving automobile when it was in collision with another car and her abdomen struck a telephone pole with great force. When she arrived in the hospital she was in severe shock and died shortly thereafter. The diagnosis was ruptured abdominal viscus, probably spleen, and massive intra-abdominal hemorrhage. Time was insufficient for operation. Autopsy revealed a complete longitudinal rupture of the body of the uterus, about 24 cm. in extent, with the baby and placenta in the abdomen.

Those cases in which rupture occurred after prolonged labor followed the usual pattern and require no special comment. On the other hand, the case in which accouchement forcé was responsible is such a tragic example of bad obstetrics that a summary should be given.

A 36-year-old, white, para 8-0-0-6, went into labor at term at 5 P.M. She was seen by her physician two hours later at which time the pains were regular and five minutes apart. She was given two injections (pituitary?) after which the doctor introduced his hand into her vagina and told her he was "opening her womb." The injections had made her pains much harder, but suddenly they ceased and patient stated that she "felt funny." She was then sent to the hospital for "instrumental delivery." Condition was rather good upon admission and the head was at the level of the spines with no cervix felt. A simple midforceps was done and patient delivered of a stillborn baby. Bleeding followed delivery, and, exploring the uterus, a rent was found extending upward from the internal os into the fundus. Hysterectomy was done and the patient recovered.

To conserve time and to prevent useless repetition it would appear wise to insert several tables at this point and to discuss them briefly and collectively.

From a study of the tables several facts appear to be rather self-evident and need only a statement of fact: Complete ruptures are more often fatal than incomplete, both to the mother and child, ruptures occurring at home carry twice the risk of those occurring in the hospital where prompt treatment

TABLE III. SITE OF RUPTURE

Upper segment	15
Lower segment	20
Both	9
Not stated	1

TABLE IV. TYPE OF RUPTURE

		MOTHER		BABY	
		REC.	DIED	BORN ALIVE	STILLBORN
Complete	36	17	19	5	32
Incomplete	9	9	0	7	3

TABLE V. TIME OF RUPTURE

		MOTHER		BABY	
		REC.	DIED	BORN ALIVE	STILLBORN
During pregnancy	7	6	1	3	4
During labor	27	14	13	7	22
During delivery	11	6	5	2	9

TABLE VI. PLACE OF RUPTURE

		MOTHER		BABY	
		REC.	DIED	BORN ALIVE	STILLBORN
Ruptured at home	21	8	13	1	20
Ruptured in hospital	24	18	6	11	15

TABLE VII. PREOPERATIVE DIAGNOSIS

Rupture	23
Placenta, premature separation of (present in 2)	6
Disproportion cephalopelvic	2
Viscus, abdominal, rupture of	1
Placenta previa	1
Rupture of placenta, premature separation of	1
Not made	3
Not stated on history	8

TABLE VIII. TYPE OF DELIVERY

		MOTHER		BABY	
		REC.	DIED	BORN ALIVE	STILLBORN
Delivered from above	25	20	5	12	15
Delivered from below	17	6	11	0	17
Died undelivered	3	0	3	0	3

TABLE IX. TYPE OF TREATMENT

		RESULTS	
		RECOVERED	DIED
Uterus repaired	11	11	0
Uterus removed	25	15	10
Abdomen not opened	3	0	3
Undelivered	6	0	6

TABLE X. SITE OF PLACENTA IN SECTION RUPTURES

	UNDER SCAR	NOT UNDER SCAR	OUTSIDE UTERUS	NOT STATED
Classical	4	2	6	1
Low	1	2	1	0

TABLE XI. ELAPSED TIME FROM RUPTURE UNTIL OPERATION

		MOTHER		BABY	
		REC.	DIED	BORN ALIVE	STILLBORN
Immediate	6	5	1	3	3
1 to 5 hours	14	12	2	7	9
6 to 11 hours	5	3	2	1	4
12 to 23 hours	3	1	2	0	3
24 to 36 hours	3	1	2	0	3
More than 36 hours	1	1	0	0	1
Not stated	3	2	1	0	3
Undelivered	3	0	3	0	3
No operation	6	0	6	0	6
Operation for disproportion	1	1	0	1	0

TABLE XII. CAUSES OF MATERNAL DEATHS

Hemorrhage and shock	13
Infection	5
Uremia	1

TABLE XIII. PARITY

GRAVIDA	RUPTURES	RECOVERED	DIED
1	4	1	3
2	6	6	0
3	6	4	2
4	7	7	0
5	4	2	2
6	3	1	2
7	1	0	1
8	3	0	3
9	5	2	3
10	2	1	1
11	1	0	1
12	1	1	0
13	1	0	1
14	1	1	0

TABLE XIV. FETAL MORTALITY

		BORN ALIVE	STILLBORN
Ruptured at home	21	1	20
Ruptured in hospital	24	11	15
Delivered from above	25	12	15
Delivered from below	17	0	17
Undelivered	3	0	3
Operation within 6 hours	20	10	12
Operation more than 6 hours	12	1	11
Others	13	1	12
Ruptured during pregnancy	7	3	4
Ruptured during labor	27	7	22
Ruptured during delivery	11	2	9

TABLE XV. COMPARATIVE MATERNAL MORTALITY

AUTHOR	CASES NUMBER	NUMBER DIED	PER CENT
Sheldon	26	11	42.3
Burkons	45	17	37.7
Knowles	12	7	58.3
Dugger	105	65	61.9
Acken	15	7	46.6
Davis*	106	57	53.7
Sadowsky	13	6	46.1
Lynch	33	18	54.5
Potter	17	3	17.6
Eastman	53	25	47.1
Present report	45	19	42.2
Totals	470	235	50.0

*Maternal mortality given for only 106 cases.

can be instituted. In cases of rupture, delivery from below is not conducive to good results, except in unusual cases. Table II emphasizes the need for early diagnosis and the prompt institution of treatment, that is, laparotomy. In Table IX various types of treatment are compared, and at once one is struck with the excellent results obtained in those cases in which the uterus was repaired and allowed to remain in the abdomen. It should be added that these patients were all sterilized at the time of operation, since it was felt that these uteri should not again be subjected to the strain of pregnancy.

In Table XIII, the parity of the patients is considered and it can be seen that, although 23 of the 45 ruptures were in patients who had had from 0 to 3 previous pregnancies, only 5 of the 19 deaths were in this group.

While Table X is not conclusive, it is interesting, to say the least, to note the number of times the placenta was found under the site of rupture.

In Table VII it is seen that the correct diagnosis was made in only one-half of the cases prior to operation. Several facts may be responsible for this large percentage of errors: first, the condition is comparatively rare and is often not thought of, and second, these cases many times present a somewhat obscure picture. For example, in the cesarean section ruptures, the onset was frequently quiet and accompanied by a minimum of shock and vaginal bleeding. Abdominal tenderness and rather constant abdominal pain were usually present, but were at times not outstanding, and it was difficult to differentiate the cases from those of premature separation of the placenta.

Summary

Forty-five cases of rupture of the pregnant uterus are presented more or less statistically with a minimum number of conclusions and with no more comment than appears necessary to explain the tables.

References

Acken, H. S., Jr.: Am. J. Surg. **49**: 423, 1940.
Alexander, J. M.: Am. J. Surg. **56**: 379, 1942.
Bill, A. H., Barney, W. R., and Melody, G. F.: Am. J. Obst. & Gynec. **47**: 712, 1944.
Burkons, H. F.: Am. J. Obst. & Gynec. **42**: 75, 1941.
Davis, H. B.: Bull. Lying-In Hosp. N. Y. **13**: 125, 1925.
DeLee, J. B.: J. A. M. A. **115**: 1320, 1940.
Dipple, A. L., and Brown, W. H.: Am. J. Obst. & Gynec. **40**: 986, 1940.
Dugger, John H.: Pennsylvania M. J. **45**: 437, 1942.
Eastman, N. J., and Delf, Eleanor: Subm. for Public Canad. Med. Jour. **52**: 376, 1943.
Gordon, C. A., and Rosenthal, A. H.: Surg., Gynec. & Obst. **77**: 26, 1943.
Knowles, J. J.: M. Rec. **144**: 125, 1936.
Lynch, J. F.: New England J. Med. **221**: 847, 1939.
Murray, H. E.: J. Obst. & Gynaec. Brit. Emp. **35**: 327, 1928.
Phaneuf, L. E.: Am. J. Surg. **56**: 379, 1942.
Potter, Irving: Am. J. Obst. & Gynec. **19**: 289, 1930.
Reese, J. M., and Linn, R. F.: West Virginia M. J. **37**: 9, 1941.
Rickards, C. E. B.: Brit. M. J. **1**: 1359, 1938.
Sadowsky, A.: Am. J. Surg. **55**: 544, 1942.
Sheldon, C. P.: Am. J. Obst. & Gynec. **31**: 455, 1936.
Selsey, A. D.: Am. J. Obst. & Gynec. **33**: 857, 1937.

THE TREATMENT OF TRICHOMONAS VAGINITIS WITH A SULFONAMIDE COMPOUND

HELEN M. ANGELUCCI, M.D., F.A.C.S., PHILADELPHIA, PA.

(From the Department of Gynecology, Woman's Medical College of Pennsylvania, and the Woman's Hospital of Philadelphia)

THE voluminous literature which has of recent years accumulated on the subject of vaginal trichomoniasis has been authoritatively summed up by the report of the Council on Pharmacy and Chemistry of the American Medical Association in the Oct. 23, 1943, issue of the *Journal* of the Association.

Besides noting the inadequacy of much of the published data, the report emphasized the "difficulty of setting up satisfactory evaluation criteria with our present knowledge" of the subject.

The source of infection of *Trichomonas vaginalis* is still unknown—the pathogenicity of this organism is yet to be definitely proved. Thus all that can be said, after reviewing numerous publications, is that a vaginitis associated with *Trichomonas vaginalis* as a distinct clinical entity is practically universally accepted and, after consideration of the innumerable substances used in treatment, we can be even more definite in the statement that there is no specific therapeutic agent.

A scientific evaluation of methods of treatment is not to be hoped for without the use of control data, and this is practically impossible in the study of a condition which involves such wide margins of error as the cooperation of the patient, her general gynecologic and endocrine status, the possibility of repeated contaminations, the presence of associated bacterial infections, etc.

Trussell and Johnson[1] have carried out a very important series of studies of the effect on pure cultures of *Trichomonas vaginalis* in vitro of the various chemicals used in the treatment of this vaginitis. These reports are among the few truly scientific studies published on the subject. Important as they are, however, they can furnish only collateral data, for, as the authors themselves state, there are too many variable factors complicating the clinical picture. For instance, of three substances which were tested in a previous study by the writer,[2] namely, picric acid, quinine sulfate, and sodium bicarbonate, and which gave practically uniform results, only one, picric acid, was found to be trichomonacidal in these studies in vitro. Further, we note that the concentration of the therapeutic agent plays an important part in the results reported by Trussell and Johnson.[1] Sulfathiazole is reported as inactive as a trichomonacide in a 1:1,100 dilution, but as active in 20 per cent concentration in a jelly base of a particular pH.

The extreme variability shown in the reaction of different patients to the same treatment emphasizes the conviction that we are far from approaching a solution to this perplexing problem; and we have felt it necessary, therefore, to search for the method of therapy which, while giving at least as good results as any other method, does so with the least inconvenience and discomfort to the patient. We must admit that in choosing this particular compound, we were not uninfluenced by the magic word "sulfonamide," and that we were also prompted by curiosity as to what results would be obtained with a substance

that would undoubtedly have a powerful bacteriostatic action on the associated bacterial (mostly streptococcic) vaginal infection.

Method

In our previous study referred to above,[2] we had used three different types of treatment, which, while giving practically the same results, still involved some disadvantages, either because of difficulty in application or because of objection on the part of the patient on esthetic grounds. The medication we are discussing in this report appears to be free of these disadvantages. It consists of an ointment* containing 15 per cent sulfanilamide, 2 per cent allantoin, and 5 per cent lactose in a greaseless base, buffered to pH of 4.5 with lactic acid. It is expressed into the vagina by means of an applicator which delivers approximately 10 Gm. at each application, and is used twice daily by the patient, at bedtime and on arising. Blood sulfanilamide levels of less than 1 mg. per 100 c.c. of blood were found by Parks[3] in 68 patients using this preparation by the same method. The ointment is odorless, nonstaining, nonirritating, and appears to spread over the vaginal and vulvar surfaces, and to be free of the particularly annoying property of discharging from the vagina and thus necessitating the use of tampons or vulval pads.

The ease and simplicity of its application assures the cooperation of the patient and, as far as local treatment is concerned, appears to fulfill the therapeutic objective set forth by the Council, of "thoroughness and persistence with the simplest and least messy procedure."

This clinical study was conducted during 1943 and 1944 at the Gynecological Clinic of the Woman's Medical College and of the Woman's Hospital, with the addition of a number of patients from private practice.

Material

One hundred patients, 62 white, 38 Negro, showing vaginal trichomoniasis were treated. The age incidence varied from 19 to 59 years, 72 per cent being between 20 and 40 years old.

Six of these patients were unmarried, 94 married, and of the latter, 32 were infertile.

The vaginal pH (nitrazene method) ranged from 5 to 7.5.

Subjectively, 94 per cent admitted having leucorrhea, 30 complained of vulvar and vaginal discomfort with pruritus and burning, one of pruritus only, six were not aware of any vaginal discharge.

Objectively, 98 showed leucorrhea of varying degree, two had no demonstrable leucorrhea, 56 had an acute vulvovaginitis, one with numerous condylomata acuminata. Twenty-two patients had cervicitis, 34 laceration and ectropion plus erosion of cervix, 28 had a coincident pelvic inflammatory disease, 8 had myomas, and one had a procidentia.

Patients were seen for periods varying from four to ninety-one weeks. The average period of observation was thirty-one weeks. The period of actual treatment varied from four to nineteen weeks, the average being eleven weeks.

Results

The same criteria were used as in our previous study.

We considered as good results: subsidence of symptoms, disappearance of trichomonads, and return of the vaginal mucous membrane to normal, this condition of normalcy being maintained throughout at least one menstrual cycle.

We classed as recurrences, cases where the vaginitis had definitely subsided, giving what we considered a good result, and suddenly recurred even if only to a minimal degree. Recurrences were invariably associated with the reappearance of the trichomonad in the vaginal discharge.

A cure was a period of six months without treatment, with freedom from symptoms and recurrences.

A failure was a case in which the trichomonads did not disappear during the course of treatment, four weeks being considered a reasonable period of trial.

*Allantomide Vaginal Cream (National Drug Co., Philadelphia, Pa.)

The following results were obtained:

Smears became negative after one week of treatment in 80 per cent of cases, after two weeks in 13 per cent of cases, after three weeks in 4 per cent, and after four weeks in 1 per cent of cases.

Good results in 98 per cent of all cases.

Failure in 2 per cent. (In one of these all inflammatory signs and symptoms disappeared in spite of the persistence of the trichomonal infestation.)

Recurrence if treatment was stopped in 16 per cent of cases.

Cases followed less than six months and showing no recurrences without treatment for at least four weeks: 14.

Cases followed more than six months: 52. Of these 8, or 15.3 per cent, were not cured, 44, or 84.6 per cent, were cured.

Summary

One hundred cases of *Trichomonas vaginalis* infestation in nonpregnant women were treated with a lactose-allantoin-sulfanilamide compound.

Good results were obtained in 98 per cent; permanent cures in 84.6 per cent.

The method was found therapeutically satisfactory and esthetically acceptable to the patient.

References

1. Trussell, R. E., and Johnson, G.: AM. J. OBST. & GYNEC. **48**: 2, 1944.
2. Angelucci, Helen M.: AM. J. OBST. & GYNEC. **31**: 1020, 1936.
3. Parks, J.: M. Ann. District of Columbia **12**: 5, 1943.

THE TRANSMISSION OF PENICILLIN TO AMNIOTIC FLUID AND FETAL BLOOD IN THE HUMAN*

JOHN H. E. WOLTZ, M.D., AND HAROLD A. ZINTEL, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology and the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania)

THE occurrence of infection of the uterine contents in patients with prolonged labor and in those with premature rupture of the membranes may constitute an indication for chemotherapy. In these circumstances, it may be desirable to use penicillin if this drug is proved to be transferred to the amniotic fluid and to the fetus. Placental transmission to the fetus was demonstrated in a short series of patients by Greene and Hobby.[1] However, their studies did not reveal the presence of penicillin in the amniotic fluid. The present study was undertaken to determine the concentration of penicillin in the amniotic fluid and in the fetal blood after administration of the sodium salt of the drug to the mother by the intramuscular and intravenous routes, and to attempt to form a preliminary estimate of the quantitative relationships of these concentrations at various times after injection.

Method

Fifteen normal women in active labor were given sodium penicillin shortly before delivery. Eleven of these received 25,000 units of penicillin in 3 c.c. of physiologic saline solution intramuscularly. Three of the eleven patients did not deliver within three hours and,

*The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

TABLE I. CONCENTRATION OF PENICILLIN IN MATERNAL BLOOD, CORD BLOOD, AND AMNIOTIC FLUID FOLLOWING INTRAMUSCULAR INJECTION OF 25,000 UNITS EVERY THREE HOURS

	PATIENT	WEIGHT (KG.)	NO. OF INJECTIONS	MINUTES BETWEEN LAST DOSE AND DELIVERY	UNITS PER C.C. OF PENICILLIN		
					MATERNAL BLOOD	CORD BLOOD	AMNIOTIC FLUID
Group I (0-60 min.)	G. P.	69	1	13	0.312	0.039	0.039
	V. G.	49	1	14	0.312	0.000	0.000
	R. M.	83	2	46	0.078	0.000	0.000
Group II (60-90 min.)	D. D.	85	1	67	0.156	0.039	0.156
	L. M.	75	1	75	0.156	0.039	0.039
	J. D.	72	2	77	0.156	0.078	0.156
Group III (90-180 min.)	Y. D.	75	1	95	0.078	0.000	lost
	A. S.	66	1	106	0.078	0.000	0.000
	C. H.	72	2	138	0.078	0.039	0.039
	D. T.	85	1	146	0.000	0.000	0.000
	H. O.	59	1	175	0.078	0.039	lost

therefore, were given a second similar injection of penicillin at the end of the three-hour period. The results are given in Table I. In each case the interval between the administration of penicillin and the time of delivery given in Table I represents the time between the last injection of the drug and the time of delivery. Four patients received sodium penicillin in an aqueous solution of 5 per cent glucose by the continuous intravenous drip method at the rate of 10,000 units of penicillin per hour. The data for the second group of patients are given in Table II.

TABLE II. CONCENTRATION OF PENICILLIN IN MATERNAL BLOOD, CORD BLOOD, AND AMNIOTIC FLUID FOLLOWING CONTINUOUS INTRAVENOUS ADMINISTRATION OF 10,000 UNITS PER HOUR

PATIENT	WEIGHT (KG.)	TOTAL UNITS OF PENICILLIN	HOURS	UNITS PER C.C. OF PENICILLIN		
				MATERNAL BLOOD	CORD BLOOD	AMNIOTIC FLUID
E. S.*	78	200,000	20	0.156	0.156	0.156
O. J.	63	20,000	2	0.312	0.078	0.078
M. J.	65	20,000	2	0.078	0.039	0.078
H. T.	64	20,000	2	0.078	0.039	0.039

At the time of delivery, a sample of amniotic fluid was collected in a sterile container from the gush of this fluid which usually accompanies the end of the second stage of labor. After the umbilical cord was divided, a sample of cord blood was collected before the placenta separated from the uterus. During the third stage of labor or immediately thereafter, a sample of maternal blood was collected. All specimens were placed in sterile tubes which contained 65 "Toronto units" of heparin and immediately placed in an icebox. The determinations of penicillin concentration were made from four to twenty-four hours after the specimens were obtained. These concentrations were determined according to a modification[2] of the hemolysis method as described by Rammelkamp.[3]

For the purpose of interpretation, Table I has been arranged in three groups according to the interval between injection of penicillin and the delivery of the child:

Group I — 0 to 60 minutes
Group II —60 to 90 minutes
Group III—90 to 180 minutes

In Group I (0 to 60 minutes after injection of penicillin), comparatively high maternal blood levels were reached while very little of the drug was found in the cord blood or amniotic fluid.

In Group II (60 to 90 minutes after injection of penicillin), the maternal blood levels were 0.156 units of penicillin per cubic centimeter. In each case there were significant amounts of penicillin in the cord blood and in the amniotic fluid.

In Group III (90 to 180 minutes after injection of penicillin), the maternal blood levels had fallen to 0.078 unit of penicillin per cubic centimeter or below, and penicillin was not found consistently in the cord blood and amniotic fluid.

*This patient's intravenous penicillin was discontinued forty minutes before delivery and blood was taken from the femoral vein of the newborn rather than the cord.

These data suggest that the maximum concentrations in the fetal circulation and amniotic fluid are found 60 to 90 minutes following intramuscular injection into the mother.

The intravenous administration of penicillin (Table II) had been continued in each case for a period of at least two hours before delivery, and in each case there was a significant amount of penicillin present in the cord blood and amniotic fluid. The one case in which the intravenous administration of penicillin had been continued for twenty hours, the maternal blood, infant blood, and amniotic fluid showed identical concentrations (0.156 unit per cubic centimeter). There was no evidence of penicillin toxicity to either mother or child in this case or in any of the other patients.

The fact that adequate penicillin levels can be produced in the amniotic fluid as well as in the maternal and fetal circulations suggests the use of penicillin in the treatment of certain types of intrauterine infection as well as its prophylactic use following premature rupture of the membranes and during prolonged labor. The dosage, mode of administration, and efficacy in these complications of pregnancy remain to be determined by future investigations.

Conclusion

Penicillin was found to be present in the amniotic fluid following the intramuscular and intravenous administration of the sodium salt of penicillin to the mother. The concentrations were comparable with those of the maternal and fetal circulations.

References

1. Greene, H. J., and Hobby, G. L.: Proc. Soc. Exper. Biol. & Med. **57**: 282, 1944.
2. Beyer, K. H., Peters, L., Woodward, R., and Vervey, W. F.: J. Pharmacol. & Exper. Therap. **82**: 310, 1944.
3. Rammelkamp, C. H.: Proc. Soc. Exper. Biol. & Med. **51**: 95, 1942.

THE EFFECT OF IRRADIATION ON THE FUNCTION OF THE OVARY IN YOUNG GIRLS

Supplementary Report

IRA I. KAPLAN, M.D., B.Sc., NEW YORK, N. Y.

(From the Radiation Therapy Department, Bellevue Hospital)

IN 1939[1] I reported the history of a case of a young girl who, at the age of 4½ years, received intensive irradiation, x-ray, and radium treatments for a pelvic tumor and who, in spite of this intensive irradiation, subsequently at the age of 12 years had normal menstruation. She continued to menstruate regularly until the age of 19 years. My reason for reporting this case at that time was to show that unwarranted apprehension was present in the minds of the clinicians regarding the effect of irradiation in girls and young women.

This present report is to bring this case to a final conclusion, albeit an unfortunate one.

On July 2, 1943, the patient reported to me, complaining of a painful area on the right side of the coccyx which made sitting down extremely uncomfortable. This condition had existed for about six months, continually growing worse, before she sought relief. On examination, I found a firm, regular, round nodule at the base of the spine to the outer border at the gluteal margin. The mass was extremely tender, not attached to the skin but not too firmly attached to the underlying tissues. It was not compressible. From July 2 until July 27 x-ray therapy was administered to the mass with apparent relief of symptoms. The patient was not seen again until Oct. 19, 1943. She had no complaints and there was no interruption of the normal menstruation. On Nov. 9, 1943, she again

reported increasing pain at the coccyx area on sitting down. Examination showed persistence of the tumor which was, however, still fairly movable. Surgery was advised and the tumor was removed on Nov. 11, 1943. Grossly, it consisted of a regular, round, semi-firm mass, encapsulated in a thin glistening fibrous cover. A cut surface showed a firm homogeneous grayish-white tissue.

Pathologically the neoplasm proved to be a neurogenic type tumor. Microscopic examination revealed a new growth composed of interlacing bundles of connective tissue and nerve fibers. In between were numerous, generally large, ganglion cells which occurred either singly or in groups. The tumor was a ganglial neuroma and apparently represented a metastasis of a malignant sympathicoblastoma.

The wound healed spontaneously and relief was given for a short time. Recurrent pains became very distressing and a course of x-ray treatment from Nov. 23, 1943, to Dec. 17, 1943, failed to give relief. X-ray therapy was again instituted in March, 1944. On April 7, 1944, she was again examined and a large tumor was felt through the rectum firmly filling the right pelvis. Surgical removal was advised. She was operated upon at the Roosevelt Hospital on April 24, 1944, but the tumor could not possibly be removed.

Microscopic examination was reported as follows: Sections from the central portion of the tumor reveal much degeneration and some necrosis. Peripheral areas of the sections reveal large cells with irregular cytoplasmic outlines. These cells have several nuclei, sometimes peripherally arranged. The nuclei are uniform in appearance, round, and frequently have a large nucleolus surrounded by a clear zone in the cytoplasm. The latter, stained with crystal violet reveals coarse granules of the Nissl body type. From the peripheries of these cells a number of fine fibrillary processes are given off. The intercellular material is made up of such fine fibrillary material. Other cells are oval and spindle-shaped, possessing bipolar fibrillary processes. In these areas no mitotic figures are seen.

A second type of structure is evident in other sections. The tumor reveals greater cellularity. The cells are oval and spindle-shaped. The fibrillary processes are less distinct. The nuclei are hyperchromatic. An occasional mitotic figure is seen. The cells are arranged in bundles of irregular size. A slight tendency to palisade arrangement of nuclei is present in some areas. Much necrosis is present in some of these areas. Blood vessels have well-formed walls.

This tumor is a ganglioglioneuroma that has undergone malignant neurinoma (neurogenic sarcoma, graded I).

The wound failed to heal, and on May 29, 1944, another piece of tissue was removed for examination and was reported as follows: Sections reveal ulceration and necrosis. Underlying structure is a neoplastic growth composed of spindle cells. Nuclei are large, rich in chromatin, oval in shape. Cytoplasm is granular, stained pink in color. Mitotic figures are present in moderate numbers; as many as 6 may be seen per high-power field. Cytoplasmic processes are short. Tumor is vascular. In some areas tumor cells are intimately associated with the capillary walls. In some areas there is palisade arrangement of nuclei. The diagnosis was spindle-cell sarcoma, neurogenic type, of buttock.

The patient persistently went downhill in spite of all measures taken, including x-ray therapy, and she died on Sept. 8, 1944. Autopsy in relation to the tumor was as follows:

The rectum is displaced anteriorly. Its wall is fixed to the capsule of the tumor by firm fibrous tissue. The mucosa is intact. On section, the muscularis and mucosal layer of the rectum are clearly visible and not involved. Bulging into the pelvis is a large, moderately firm, whitish lobulated tumor mass that measures about 15 cm. in greatest diameter. The capsule over it is smooth. The tumor mass is continuous with the large fungating mass partially necrotic that protrudes over the sacral area. The rectum and anal orifice are not involved. The skin is intact but it is displaced anteriorly. The tumor reaches to within 1½ cm. of the anal margin on the skin surface. The rectum is not distended. On multiple sections the tumor mass in some areas shows marked degeneration, pseudo-cyst formation, with lobules filled with clear fluid. In other areas the tissue is pale grayish-white in color; it is rather tough in consistency. The exposed portion of the tumor reveals large areas of dirty grayish necrosis and adjacent areas of hyperemia and hemorrhage.

Reference

1. Kaplan, Ira I.: Am. J. Obst. & Gynec. 37: 158, 1939.

METASTATIC ADENOCARCINOMA OF THE CERVIX UTERI ASSOCIATED WITH PRIMARY GASTRIC CANCER

EDWIN L. WILLIAMS, M.D., NASHVILLE, TENN.

(From the Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine)

ATTENTION was first directed to the relationship between malignant neoplasms of the gastrointestinal tract and secondary pelvic cancer in 1896 by Friedrich Krukenberg.[1] He described a tumor of the stomach associated with an ovarian neoplasm and designated the ovarian tumor "fibrosarcoma ovarii mucocellulare (carcinomatodes)." It is now well known that the "Krukenberg tumor" represents secondary carcinoma of the ovary associated with a primary colloid carcinoma of the gastrointestinal tract usually occurring in the stomach.

The primary location of the tumor has been variously described throughout the alimentary tract from the esophagus to the sigmoid.[2, 3] The ovary, however, has uniformly been the seat of the secondary lesion. It is the purpose of this paper to describe a carcinoma of the cervix uteri occurring in association with a carcinoma of the cardiac portion of the stomach.

Case Summary

Mrs. M. J., a 32-year-old multipara, was admitted to Vanderbilt University Hospital, Aug. 28, 1944, with the chief complaint of persistent vomiting. Her present illness began ten months before admission and was initiated by nausea during meals followed by emesis of at least a portion of each meal. During the ten months prior to admission her weight decreased from 259 pounds to 134 pounds. She became extremely weak and was able to be out of bed only with difficulty.

She complained of pains in the lower abdomen which were never excruciating. Her menses had been regular in interval and flow but had increased somewhat in duration during the two or three months prior to admission to the hospital. She had recently noted mild dysmenorrhea. There was no history of severe menstrual pain. She had had no vaginal discharge. There was a history of mild intermittent constipation. Hematemesis and melena were absent.

General physical examination revealed evidence of recent weight loss but no other significant findings. Pelvic examination showed normal external genitalia. On bimanual palpation, the cervix, the fornices of the vagina, the anterior vaginal wall, and the parametria were found to be "woody" in consistency. The cervix was firmly fixed so that on manipulation all the surrounding structures moved with it. There was no evidence of ulceration or infection, but hemorrhage from the os was evident on inspection. The fundus of the uterus was normal in size, but was abnormally firm in consistency. There was no palpable enlargement of the tubes or ovaries. There was no intrinsic lesion of the rectum.

Esophagoscopy revealed a dilatation of the entire esophagus most marked in its lower third. Marked hyperemia of the entire esophageal wall was evident. An obstruction was found at the level of the diaphragm and there was apparently an infiltration of the wall in this area by a neoplastic process which had produced small areas of ulceration. A specimen was taken from this area for microscopic study.

Subsequently, the cervix was exposed and tissue was removed for examination. The cervix was indurated and bled freely when incised.

Cystoscopy revealed hyperemia of the bladder wall. The ureteral orifices appeared normal and ureteral catheters were easily passed.

Gastrointestinal roentgenography following a barium meal failed to demonstrate a lesion of the stomach or the small intestine.

Thirteen days after admission an exploratory laparotomy was performed. Examination of the stomach revealed a nodular mass high on the lesser curvature which extended into the esophageal hiatus. There were numerous small nodules scattered over the peritoneal surface

of the diaphragm. There was no apparent involvement of the liver. Nodules were scattered profusely over the surface of the peritoneum along the lateral pelvic walls, the surface of the ovaries, the omentum and the fundus of the uterus. The ovaries were not enlarged but were adherent to the posterior leaves of the broad ligaments.

Fig. 1.

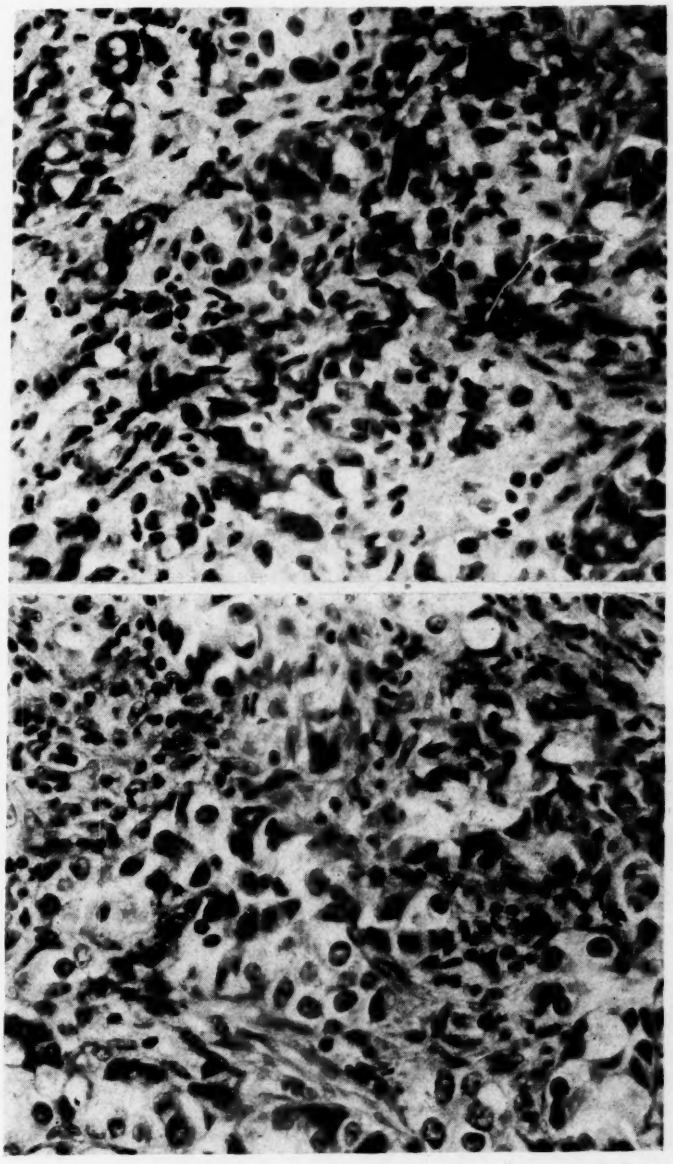

Fig. 2.

Fig. 1.—Primary adenocarcinoma of the stomach (×500).
Fig. 2.—Secondary adenocarcinoma of the cervix uteri (×500).

Biopsies were made from the lesion of the stomach, the omentum, and the peritoneal nodules. A gastrostomy was performed and the abdomen closed. The patient's postoperative course was uneventful.

Microscopic sections from the gastric lesion, the peritoneal metastases, and the cervix presented strikingly similar characteristics. The primary lesion consisted of anaplastic epithelial cells varying somewhat in size, shape, and arrangement and containing hyperchromatic nuclei. The nuclei in many of the cells were located eccentrically and were crowded

against the cell membrane, producing a "signet ring" appearance. An adenomatous arrangement of cells was present in some areas but was not uniform throughout. The stroma contained numerous small blood vessels. Sections from the peritoneal nodules and from the cervix were similar. The stroma of the cervical tumor was relatively more abundant and somewhat more dense but the epithelial characteristics were uniform throughout. The glandular arrangement of the cells and the mucoid content were remarkable.

The patient did not return to this Hospital inasmuch as she lived a great distance away.

Summary

1. Secondary adenocarcinoma of the cervix uteri may occur in association with a primary gastric cancer.

2. A case is presented which demonstrates this pathologic entity.

The author wishes to express appreciation to Dr. Lucius E. Burch, Obstetrician and Gynecologist-in-Chief, to the house staff, and to the members of the Departments of Surgery and Pathology who aided in the study and care of this patient.

References

1. Krukenberg, Friedrich: Arch. f. Gynäk. **50**: 287, 1895-96.
2. Major, Ralph H.: Surg., Gynec. & Obst. **27**: 195, 1918.
3. Chapman, T. L.: Surg., Gynec. & Obst. **31**: 58, 1920.

TERATOMA OF THE PERINEUM IN A NEWBORN INFANT*

A. F. Lash, Ph.D., M.D., Chicago, Ill.

(From the Department of Obstetrics and Gynecology and Pathology, Michael Reese Hospital and University of Illinois)

EMBRYONIC new growths of the perineum are rare. Thus under the heading "sacrococcygeal tumors" in Abt's *System of Pediatrics*, Schultz states that mixed tumors arising at the caudal pole of the embryo are more numerous than those of the cranial pole. They may be situated within the pelvis, anterior to the sacrum and coccyx and behind the rectum; posterior to the bony structures and beneath the skin; or rarely, in the perineal region.

Schwalbe's classification of sacrococcygeal tumors is as follows:

I. A parasitic mass with more or less well-developed limbs or organs (pyopagus parasiticus).

II. An external tumor is present, but organs or parts of organs are present only within the mass.

III. Teratomas with derivatives of the three germ layers.

IV. Mixed tumors with derivatives of only two germ layers, usually ectoderm and mesoderm.

Report of a Case

A female child, weighing 4 pounds, 12 ounces, was delivered in the thirty-sixth week of pregnancy, after six hours of labor, by prophylactic outlet forceps and episiotomy. The mother, a 35-year-old white gravida v, para o, gave a history of healed pulmonary tuberculosis, two induced abortions, one spontaneous abortion, and one twenty-week pregnancy terminated by abdominal hysterotomy because of placenta previa.

Examination of the infant revealed a normal development except for a red, glistening, smooth, cylindrical mass, about 2.5 cm. long and about 1 cm. in diameter, extending from the perineum just below the fourchette (Fig. 1). There was no communication with either

*Presented before The Chicago Gynecological Society, March 17, 1944.

Fig. 1.

Fig. 2.

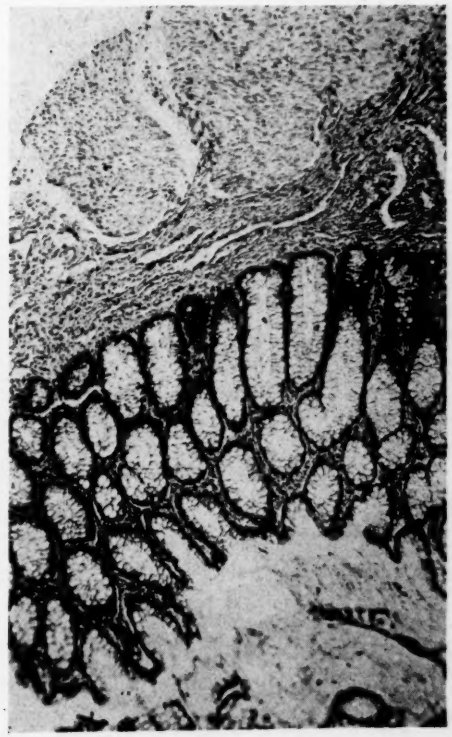

Fig. 3.

the vagina or the rectum. On the twelfth day after delivery, the mass was resected and the skin edges brought together. The wound opened on the sixth postoperative day but remained clean and closed by secondary intention. The baby has continued to thrive and develop normally.

Microscopic examination showed the external surface of the mass to be connective tissue with muscle fibers surrounding a cavity lined by glands resembling rectal mucosa (Figs. 2 and 3).

The teratoma in this instance was a mixed tumor consisting of derivatives from the entoderm and mesoderm and located in a rarely seen location, the perineum.

References

1. Abt, Isaac A.: A System of Pediatrics, Philadelphia, 1926, W. B. Saunders Co., Vol. III, p. 726.
2. Schwalbe, Ernst: Morphologie der Missbildungen, Jena, 1909, Gustav Fischer, Vol. III, p. 234.

30 North Michigan Avenue

Department of Reviews and Abstracts

Selected Abstracts

Pregnancy, Complications, Etc.

Leon, J., Lascono, Gonzales, J. M., and Leon, C. T.: Hematomola of Breus. Diagnostic Difficulties Increased by the Biologic Reactions, Rev. Asoc. méd. argent. **57:** 1108, 1943.

The authors report a case in a girl, 17 years of age, in whom the evolution of pregnancy seems to have been arrested between the sixth and eighth weeks, and retention in the uterine cavity was over seven months. The embryo had completely disappeared without even leaving traces of the umbilical cord. The most extraordinary observation was the positive result of three Friedman tests which increased the diagnostic difficulties. The authors emphasize the advisability of subjecting to critical judgment the results of the biologic tests. A positive result does not allow exclusion of a mole of Breus. Nor is it possible to fix within strict limits the hormonal rates which correspond to a normal pregnancy and to the various pathologic processes. In a case of discrepancy between clinical judgment and laboratory tests, the latter should be repeated, and the results of the clinical examination must principally be taken into account.

J. P. GREENHILL.

Bunster, Eduardo: Pregnancy at Term After Partial Hysterectomy, Bol. Soc. chilena de obst. y ginec. **8:** 400, 1943.

The author had not found any such case in the literature at his disposal. The patient, 27 years of age, had been operated upon for a fibromyoma, 8.5 cm. in diameter, and the uterus had been reconstructed from its posterior wall and lateral borders. The author feared rupture of the organ during pregnancy and especially during labor. He calls attention to the capacity for regeneration of the uterus which, at the end of pregnancy, was nearly normal size and form. The organic adaptation was undoubtedly facilitated by the oligohydramnios which allowed maximal use of the available space for the fetal development. However, this space was slightly insufficient as shown by a slight facial asymmetry with which the child was born.

J. P. GREENHILL.

Varas, Osvaldo: Treatment of Nausea and Vomiting of Pregnancy With Vitamin B_6, Bol. Soc. chilena de obst. y ginec. **8:** 404, 1943.

The author has used vitamin B_6 ampules of the Biochemical Laboratory Valparaiso, containing 5 mg. Injections were given intramuscularly every two to four days and their number varied from two to six, two being sufficient in most cases to obtain a definite result.

Seventeen patients were treated: all had nausea and vomiting and some were in serious condition. Twelve were immediately relieved by the first injection and all disturbances were stopped by the second. Relief in the other patients was also obtained, although more slowly. The action of the drug is so immediate and constant that, if it does not occur, it is well to suspect that some other disease is masquerading under the picture derived exclusively from the pregnancy.

In two cases, abortion occurred at least 15 days after the termination of treatment. The author does not think that there was any relation between the treatment and the abortion. One of the patients had previously had a spontaneous abortion.

J. P. GREENHILL.

MacLennan, Hector R.: A Case of Osteomalacia in Pregnancy, J. Obst. & Gynaec. Brit. Emp. **51:** 127, 1944.

The author presents a case of acute osteomalacia complicating pregnancy. Blood studies are mentioned, as well as the dietary deficiency in this patient. Some facts, pro and con, are mentioned with reference to the comparison between rickets and osteomalacia.

WILLIAM BERMAN.

Russo, A. J.: Nausea and Vomiting of Pregnancy Treated With L-Histidine Monohydrochloride—Preliminary Report, Virginia M. Monthly **71:** 522, 1944.

The use of l-histidine monohydrochloride in the treatment of peptic ulcer suggested its use in the treatment of hyperemesis gravidarum. Five patients with varying degrees of vomiting were treated by the intramuscular injection of 5 c.c. of l-histidine monohydrochloride. Complete relief was obtained in all. The author suggests that its beneficial effect may depend upon the power of the drug to relieve the hyperemia of the gastric mucosa.

WILLIAM BICKERS.

Kilkenny, G. S.: Diabetes in Pregnancy, Wisconsin M. J. **43:** 622, 1944.

According to the author, the advent of insulin has complicated the management of the pregnant diabetic so that, although maternal and fetal morbidity and mortality have been lowered, the individual case still requires careful evaluation and attention. On the one hand, severe diabetes disturbs the metabolism of pregnancy, creating a hormonal imbalance leading either to abortion or to extremely obese babies prone to acidosis, the result of extremely high blood sugar levels. On the other hand, the pregnancy itself tends to produce acidosis in the mother, especially in the later months, with its attendant dangers. Careful attention to the size of the fetus at the eighth lunar month of pregnancy is advocated, and any evidence of excessive weight is indication for termination of the pregnancy.

The procedure for delivery is determined by the controllability of the diabetes and the energy-requirement factor of labor. In general it may be stated that a diabetic to be safely delivered by the vaginal route must have a blood sugar below 170 mg., no acidosis, and proper insulin balance. Cesarean section is strongly advocated as a prophylactic measure since it eliminates the energy-requirement factor and in this way allows for easier control of the diabetes.

FRANK SPIELMAN.

Lima, Octavio Rodrigues: Contribution to the Study of Vesicular Mole, An. brasil. de ginec. **18:** 1, 1944.

The author describes the formation of the normal chorionic villi and the hormonal activity of the ovum, once it is fixed to the maternal organism, to facilitate the explanation of what occurs when vesicular mole develops. On the basis of the histologic study of his cases and of physiologic considerations, he supports the theory of vascular aplasia in the pathogenesis of vesicular mole rather than that of a degenerative process or chorionic neoplasm.

Histological examination of an expelled mole to evaluate its malignancy is superfluous because spontaneous expulsion alone is proof that at least these fragments are inactive. Examination of a surgically removed mole to deduce possible malignancy from its cytologic aspect is senseless because the curette or the finger removes only the part that was already prepared for elimination by cleavage. The cells retained in the depth of the uterine wall are those which will proliferate and present the characteristics of a neoplasm. Therefore, it is preferable to remove

the uterus which contains atypical and active chorionic elements, even though they do not yet have a clearly malignant character, rather than to preserve it in the vain hope that the trophoblastic activity will cease. It would seem that the intervention of a hormonal disequilibrium is necessary to cause the appearance of malignancy.

J. P. GREENHILL.

Smith, O. W., Smith, G. van S., and Hurwitz, D.: The Relationship Between Hormonal Abnormalities and Accidents of Late Pregnancy in Diabetic Women, Am. J. M. Sc. **208**: 25, 1944.

Previously reported studies from the authors' laboratory have indicated that an abnormal rise in the chorionic gonadotropin (C.G., A.P.L., prolan) of the blood serum occurs in pre-eclampsia and eclampsia in both diabetic and nondiabetic women four to eight weeks prior to the appearance of any clinical signs. Although it is the most easily detected change, it is not as consistent a finding as urinary evidence of a changed metabolism of the placental steroids involving a progressive deficiency of estrogen and progestin.

Hormonal studies in sixteen pregnant diabetic women were made, starting between the sixteenth and twenty-ninth weeks. Of these, only eight had normal offspring, and in fifteen some accident of late pregnancy occurred. Serum chorionic gonadotropin was repeatedly measured in all of the patients, and in eight the metabolism of the placental steroids was also investigated by repeated urinalysis for metabolites of estrogen. The results show that an abnormal rise in serum C.G. does not always precede the accidents of late pregnancy which so frequently are seen in diabetic women, especially those involving death of the fetus. Premature withdrawal of estrogen and progestin, however, was a consistent finding in abnormal cases and an immediate precursor of either toxemia or death of the fetus. This change was preceded by such a marked increase in the production of the placental steroids that it could be recognized at least ten weeks prior to the clinical accident and five weeks before any rise in serum C.G. took place. To forestall the premature withdrawal of the placental steroids leading to the appearance of toxemia, a constant daily supply of estrogenic material may conceivably postpone the withdrawal until the maternal and fetal organisms are ready for delivery.

FRANK SPIELMAN.

Puerperium

Rotstein, Morris L.: Getting Patients Out of Bed Early in the Puerperium, J. A. M. A. **125**: 838, 1944.

The author chose 150 patients at random who were delivered vaginally and allowed them up on the third and fourth day after delivery. Parity and type of delivery were not taken into consideration. No patient with any complication of pregnancy was included in this group. No ill effects were noted in this series. When allowed up, the patients felt well and were able to walk about and take care of themselves. They were allowed home from the sixth to the eighth day postpartum. A routine of postpartum care is outlined in the author's report. The patients are allowed up if the temperature for the preceding twenty-four hours is 99.6° F. or less. Involution of the uterus was accelerated and uterine prolapse was not encountered. The healing of episiotomies was not affected by this procedure. No cases of thrombophlebitis were noted.

WILLIAM BERMAN.

White, Robert A.: Puerperal Sepsis Treated With Penicillin, South. M. J. **37**: 524, 1944.

A multipara, aged 25 years, went into spontaneous labor and promptly began to bleed from the vagina. Examination revealed a transverse presentation with shoulder presenting. Labor continued for fifteen hours, and at this time the cervix,

or that portion remaining, since a high amputation had been done previously, was three fingers dilated. A piece of placenta was palpable in the cervical os. Under ether, the cervix was dilated and a version accomplished. Profuse bleeding followed and the placenta was removed manually. The patient was in shock. Antishock therapy was instituted. The next day brought a temperature and chill following which the patient went into a typical puerperal sepsis which did not respond to transfusions, and a total dose of sulfadiazine, 25 Gm., over a period of several days, was administered without effect. When the patient appeared moribund, a supply of penicillin was obtained and given intravenously and intramuscularly. A total dose of 500,000 units over a period of forty-eight hours was given. Recovery was prompt and sustained.

WILLIAM BICKERS.

Radiation

Willan, R. J., and Shaw, Bernard, A. F.: A Case of Utero-Vesical Fistula After Radium, Brit. J. Surg. **31**: 404, 1944.

The author reports a case of uterovesical (cervix) fistula which followed the use of radium in the treatment of metrorrhagia. The fistula was closed by a combined intraperitoneal and intravesical approach done in two stages. The patient made an uneventful recovery except to the extent that she lacked full bladder control when standing or walking when last seen by the doctor.

WILLIAM BERMAN.

Pohle, E. A.: Sterilization of the Ovaries by Roentgen Rays in the Treatment of Distant Metastases From Primary Carcinoma of the Breast, Am. J. Surg. **54**: 490, 1941.

The effect of sterilization of the ovaries on metastatic carcinoma from a primary focus in the breast is discussed. Two cases demonstrating the efficacy of the treatment are reported. X-ray castration of all women regardless of age who have metastatic carcinoma from a primary carcinoma of the breast, as well as of all women 40 years of age or older who show no metastases following operation, is recommended. The author states that "the mechanism of the effect is not exactly known although there seems to be little doubt that the withdrawal of the hormones is responsible to a large extent."

FRANK SPIELMAN.

Molinari, Jose Luis: Roentgen Therapy in Ovarian Insufficiency, Obst. y ginec. latino-am. **1**: 359, 1943.

Roentgen rays obey the general law of Arndt and Schultze, i.e., the same therapeutic agent acts as a stimulant in small doses, as an inhibitor in moderate doses, and with destructive effect in large doses. There is as yet no experimental proof that radiation produces excitation or stimulation directly, but indirect radiostimulation is accepted by most authors and may be produced by various mechanisms.

The author presents an exhaustive review of the literature and summarizes the practical clinical considerations. According to Wolf, there are three principal causes of amenorrhea: (1) depressed function of the anterior pituitary lobe; (2) excessive quantity of stimulating estrogenic hormone, causing formation of single or multiple cysts without formation of corpus luteum; (3) excess of gonadotropic luteinizing hormone. In group 2, the endometrium is hyperplastic (polyhormonal amenorrhea of Zondek), and in group 3 it is in the premenstrual phase. Roentgen therapy over the pelvis will produce no results in group 1, but treatment of the pituitary is effective. In group 2, roentgen rays destroy the persistent follicles and yield good results. In group 3, destruction of the persistent corpus luteum causes menstruation in a premenstrual endometrium.

For irradiation of the ovaries, small doses of high voltage are employed. The technique usually recommended is 20 kv., 4 Ma., filter of 0.5 mm. copper, with addition of 1 mm. of aluminum, and a focal distance of 30 to 40 cm. The treatment

is administered to anterior and posterior pelvic fields, right and left, or a single pelvic field of greater size, anterior and posterior. When four fields are used the size is 8 by 10 or 10 by 15, and for two fields, 20 by 24 cm.

For irradiation of the pituitary, two lateral fields (6 by 8 cm.) are used. The dose is 75 to 150 r. (measured in air).

The first week, the pelvis is irradiated anteriorly; the second week on the posterior fields; and the third week again on the anterior fields. In rare instances, a fourth treatment is administered. Irradiation of the pituitary can be carried out at the same time as anterior irradiation of the pelvis.

Stimulating ovarian and hypophyseal irradiation produces favorable results in a high proportion of cases, many of which have been subjected to radiation treatment as a last resort. The dose administered for stimulation does not produce any unfavorable change in the mother or in children that might be born subsequently. Roentgen rays in stimulating doses administered with proper technique are a most effective agent in treatment of amenorrhea and sterility due to ovarian insufficiency.

J. P. GREENHILL.

Kenny, Meave: The Clinically Suspect Pelvis and Its Radiographical Investigation in 1,000 Cases, J. Obst. and Gynaec. Brit. Emp. **51:** 277, 1944.

This report concerns the clinical roentgenologic correlation in 1,000 women which were classified as "suspect" problems for labor. The roentgenologic technique used was quite flexible, used to conserve on films. Dr. Kenny suggests the term "pithecoid" for the so-called "anthropoid" type, in order to convey, fitly, the sense "ape-like," and feels that a morphologic classification is essential in the analysis of the variable forms adult pelves may display.

In over 80 per cent of the cases, the promontory was not reached and, as shown by radiographs, a false impression of pelvic adequacy at the brim might have been gained from clinical examination. The author also believes that vaginal examination in late pregnancy is more valuable for eliciting the shape of the lower fore-pelvis and lower sacral region, than for its popularly avowed purpose, the estimation of the diagonal conjugate. The short android hind pelvis plays an important role in dystocia. Although the author believes it is important to determine the intertuberous diameter and the width of the subpubic arch, it was interesting to note a small incidence of operative delivery when the lower fore-pelvis is narrowed and the hind pelvis adequate, as in the gynecoid-android type.

Prognosis regarding the probable outcome of labor, based upon the fetal pelvic relationship and pelvic conformation as revealed by roentgenograms, proved accurate and practical. This fact became helpful in an understanding of the principles of labor mechanism for standard pelvic types, useful in operative delivery and for teaching purposes. This point is particularly apparent from the successful use of Barton forceps in transverse arrest of the head in several instances.

From a small study series, a suggestion is offered that there may be a mother-daughter affinity in pelvic form. The author also concludes that a certain relationship between body build and pelvic shape exists. The android type was found to show a predisposition to develop toxemia of pregnancy, an observation also relating to the dystocia syndrome types of patient. It is of interest to note the incidence of rickets in Londoners (5 cases in 1,000), and osteomalacia (1 case), an incidence considerable lower (for rickets), than exists in this country.

During the six-year period devoted to the study, 10,000 women were delivered in the hospital and 94.8 per cent delivered spontaneously. The greater number of the operative deliveries from this large group occurred in the 1,000 cases selected for this report. However, the infant loss occurring in the operative group compared favorably with the low rate obtaining from all births in the unit.

The results of the study revealed the value of pelvic radiography in the diagnosis and treatment of obstetric difficulty due to malpositions or to pelvic abnormalities.

HOWARD C. MOLOY.

Contraception, Fertility, Etc.

Pommerenke, W T.: The Sterility Problem, West. J. Surg. 52: 295, 1944.

Requirements for pregnancy are: ovulation, spermatization, insemination, conjugation, migration, and nidation. The ovary must yield normal ova, normal spermatozoa must be produced and deposited near the cervical os, the uterotubal tract must permit union of egg and sperm and allow passage downward of the fertilized ovum, a healthy and prepared endometrium must await the fertilized ovum, and the nidation must persist for a period sufficiently long for the fetus to become viable. More frequent than those cases with some absolute sterility factor are those due to a summation of subthreshold defects.

About 12 per cent of all couples are involuntarily sterile and in these one will find a male defect in about 30 per cent. Study of the female should not be undertaken until the status of the male has been determined. Defects in spermatogenesis and obstruction of the vas are the most common male defects. Failure to produce normal ova and some mechanical obstruction in the uterotubal canal are the most common in the female. Immunization of the female by her husband's sperm with production of a spermatotoxin is suggested, and the early destruction of the ovum in a mother with anti-Rh agglutinins must be considered. A favorable environment for survival and motility of the sperm is provided by a glucose-saline douche just before coitus. Congenital hypoplasia of any part of the genital tract is a difficult sterility factor to combat. Study must include the Rubin test, basal metabolism, glucose tolerance, endometrial biopsy, and Huhner tests.

WILLIAM BICKERS.

Grafenberg, Ernest, and Dickinson, Robert L.: Conception Control by Plastic Cervix Cap, Western J. Surg. 52: 335, 1944.

A small plastic cap that adheres by a broad edge to the vaginal fornices is equal to the rubber diaphragm in its effectiveness as a contraceptive device. Clinical experience with this cervix cap has been extensive in Europe, and favorable reports from several well-known gynecologists are quoted. The cap may be inserted by the patient for a single coitus or may be left in place over a period of several weeks without discomfort or injury to the tissues. Follow-up on a large series of patients by these authors reveals only a slight redness about the fornices after the cap has been in place for several weeks and no permanent damage has been observed nor has any impediment to fertility upon discontinuance of its use been noted. It affords excellent protection against infection of the cervix from the vagina. Removal may be practiced after each coitus or it may be left in place and removed only during menstruation. The authors recommend a plastic cap available in three sizes which will meet all requirements. Especially is it indicated in those patients with cystocele or very short vaginal fornices where the diaphragm is unsatisfactory. It is also noted that some patients complain of discomfort with the diaphragm and occasionally the woman fails of the orgasm because the diaphragm covers the erogenous area just beneath the urethra. The properly placed cap cannot be displaced by the thrust of the penis.

WILLIAM BICKERS.